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Iron-Deficiency Anemia in Infant Development: Implications for Growth, Cognitive Development, Resistance to Infection, and Iron Supplementation

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ABSTRACT Iron plays an important role in many metabolic processes, including oxygen transport, oxidative metabolism, and cellular growth. During infancy, inadequate supply of iron resulting in iron-deficiency anemia is associated with morbidity, impaired growth, and decreased behavior and psychomotor development. Although iron requirements during infancy have become better defined, iron-deficiency anemia persists as one of the most common health problems worldwide, a condition that affects approximately 20–25% of the world's infants. Today, much attention is being given to not only preventing iron-deficiency anemia but also to avoiding excessive iron supplementation. There is concern that excessive and widespread iron supplementation could lead to decreased resistance to infection and promotion of gastrointestinal illnesses. However, the literature on the relationship between iron status and chronic infection and disease contains conflicting viewpoints. Some investigators contend that mild iron-deficiency is beneficial for immunity whereas others argue that any deficits in iron status are detrimental. Iron absorption and metabolism are influenced by interactions between iron and other dietary nutrients. Many components of the diet act to inhibit or enhance iron absorption; this information is critical for food fortification programs designed to prevent iron-deficiency anemia worldwide. This paper reviews some of the biological characteristics of iron metabolism and absorption, iron needs during infancy, interactions of iron with other nutrients, methods for hematological assessment, iron-deficiency anemia and growth, the relationship between iron-deficiency anemia and infant psychomotor development, and the impact that iron supplementation has on resistance to infection and gastrointestinal illnesses. The serious consequences of iron-deficiency anemia for infant health, behavior and development, and the widespread prevalence of this disorder are reasons for its prevention. The benefits of oral supplementation of iron appear to outweigh the possibility of iron excess during infancy, a period of rapid growth and development characterized by a marginal dietary supply of iron. Yrbk Phys Anthropol 40:25–62, 1997. © 1997 Wiley-Liss, Inc.

Iron deficiency, the primary cause of anemia, is the most common nutritional deficiency in the world. The World Health Organization (deMaeyer and Adiels-Tegman, 1985) estimates that iron deficiency affects nearly two billion people in developed and developing countries. Iron deficiency is particularly prevalent among infants and young children because rapid growth imposes large iron needs when the diet typically contains a marginal supply of iron. In developing countries, about half (51%) of children younger than 5 years of age are anemic (deMaeyer and Adiels-Tegman, 1985). In the United

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States, the prevalence of iron deficiency and iron-deficiency anemia is now relatively low. Data from the third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) indicate that 9% of toddlers aged 1 to 2 years are iron deficient and 3% have iron-deficiency anemia (Looker et al., 1997). However, iron deficiency and iron-deficiency anemia persist despite a good understanding of methods for its detection, prevention, and treatment.

In healthy, term infants, iron found in storage compounds such as ferritin and hemosiderin are adequate to maintain iron sufficiency for approximately 4 months of postnatal growth (Oski, 1993). Thereafter, the amount of iron in these compounds is rapidly depleted. Infants who do not receive iron supplements are at risk of becoming iron deficient, particularly during the second 6 months of life (Woodruff et al., 1977; Saarinen, 1978; Siimes et al., 1984; Hertrampf et al., 1986; Pizarro et al., 1991). Weaning diets, if they consist largely of cow milk, are often very low in bioavailable iron, and the iron from vegetables may be poorly absorbed because of the inhibiting effects of calcium in cow milk, phytates in flour, or low levels of ascorbic acid in the diet (Fomon, 1993).

The consequences of iron-deficiency anemia are numerous. Anemia is only one serious manifestation of iron deficiency. Iron deficiency also has been associated with delays in cognitive development and behavior during infancy and childhood (Lozoff et al., 1982, 1987, 1991, 1996; Walter et al., 1983, 1989; de Andraca et al., 1990; Idjradinata and Pollitt, 1993). Infants with chronic or moderately severe iron-deficiency anemia have shown delays in mental and motor development that persist to at least 5 years of age (de Andraca et al., 1990; Lozoff et al., 1991). However, iron-deficiency anemia can coexist with many other nutritional deficiencies and environmental risk factors. Risk factors associated with delayed infant cognitive development include low birth-weight, malnutrition, maternal depression, and low parental education level (Pollitt, 1987; Zuckerman and Beardslee, 1987; Kopp and Kaler, 1989; Lyons-Ruth et al., 1991; Breslau et al., 1994). A combination of many risk factors increases the likelihood for delayed infant cognitive development (Huston et al., 1994). For this reason, a causal relationship between iron-deficiency anemia and delays in infant cognitive development has been difficult to establish. Many studies have not been able to control for many of the biological and social characteristics of iron-deficient anemic infants.

Proper diagnosis of iron status is based primarily on laboratory procedures. Chronic disease and/or infection can result in anemia even when the diet is adequate in iron (Yip and Dallman, 1988). Mild infection may also result in anemia, leading to decreased serum iron concentration and increased serum ferritin concentration (Yip et al., 1987a). Since hemoglobin concentration is often used to screen for anemia, subjects with anemia of infection or chronic disease are often misdiagnosed as suffering from dietary iron deficiency (Arthur and Isbister, 1987; Fairbanks and Beutler, 1988). Reliance on biochemical measures including hemoglobin concentration may be inappropriate up to several weeks after a mild infection (Olivares et al., 1989). The development of a new assay, the serum transferrin receptor, has helped solve this problem. The assay is sensitive to detect mild iron deficiency and is not affected by infection (Kohgo et al., 1987; Cook and Skikne, 1989; Flowers et al., 1989). However, serum transferrin receptor cutoff values for specific age and gender subgroups have not been established.

The literature on the relationship between iron-deficiency anemia and chronic infection and disease contains conflicting data and divergent views. Some researchers have suggested that iron deficiency confers protection from pathogen or neoplastic invasion and that the resulting anemia may be an immunological defense, particularly in developing countries where chronic disease is commonplace (Kent and Lee, 1992; Kent et al., 1994; Kent and Dunn, 1996). Other researchers have argued that any inadequate supply of iron to body tissues is detrimental to immunity (Fomon, 1993; Walter et al., 1997). Understanding and determining the causes of anemia are critical, particularly when designing food fortification programs that intend to meet the iron

needs of infants and children in the United States and elsewhere.

Not only does a lack of iron pose special health problems, excessive dietary iron can have adverse effects. Animal research has suggested that large doses of iron may diminish the ability to resist gastrointestinal infections (Bullen et al., 1972; Mevissen-Verhage et al., 1985). When supplementation of breast-feeding is necessary, the administration of a low-iron formula has been considered by some to be desirable because the higher iron content of iron-fortified formula could possibly saturate the breast milk protein lactoferrin, which helps to prevent the overgrowth of intestinal *Escherichia coli* (Lawrence, 1994; Larson, 1995). However, it is still unclear whether the data from animals studies are appropriate for infants (American Academy of Pediatrics, 1978; Stockman, 1981; Humbert and Moore, 1983; Dallman, 1989; Fomon, 1993). Are breast-fed infants less susceptible to gastrointestinal problems than iron-supplemented breast-fed infants or infants fed iron-fortified formula? There is insufficient information to address this question. This uncertainty has led to controversy concerning recommendations for iron supplementation during infancy.

This paper addresses these issues by considering: the function of iron and its absorption, transport and storage; iron needs during infancy; interactions of iron with other nutrients; methods of hematologic assessment; prevalence of iron-deficiency anemia; iron-deficiency anemia and growth; the relationship of iron-deficiency anemia and cognitive development; the effects of iron supplementation on resistance to infection; the relationship between iron and gastrointestinal disturbances, and the justification for iron supplementation.

THE FUNCTIONS OF IRON

Iron compounds and their function

Iron is a constituent of hemoglobin, myoglobin, and a number of other enzymes that function to transport, store, and utilize oxygen (Dallman, 1986a). As part of hemoglobin, iron is needed to transport oxygen via the bloodstream from the lungs to the rest of the body's tissues (Dallman, 1986a). As a component of myoglobin, the red pigment of muscle, iron is responsible for the storage of oxygen used during muscle contraction (Dallman, 1990). Iron is also a component of several non-heme iron compounds (iron-sulfate proteins and metalloflavoproteins) involved in oxidative metabolism that account for most of the iron in the mitochondria. There are several other iron-dependent enzymes that do not contain iron but require iron as a cofactor or activator. These include tryptophan pyrolase and phosphoenol-pyruvate carboxykinase (Dallman, 1986a).

In addition to iron-containing compounds that serve metabolic or enzymatic functions, about 5–30% of iron is found in storage compounds such as ferritin and hemosiderin (mainly in the spleen, liver, and bone marrow). These proteins are involved in the regulation of iron homeostasis. When the supply of dietary iron becomes inadequate, iron is mobilized from ferritin and hemosiderin and is transported within the body by binding with the protein transferrin (Dallman, 1986a).

At birth, the newborn is supplied with amounts of iron in the form of hemoglobin and in iron stores to maintain iron sufficiency for 4 to 6 months (Dallman et al., 1980; Siimes, 1982). However, within the first year of life, the body weight of an infant triples and the need for iron almost doubles to meet the demand of rapid growth; iron stores contribute about 25% of this amount (Dallman et al., 1980). During the first 2 months of life, there is a marked decline in hemoglobin in response to increased postnatal delivery of oxygen to the tissues (Dallman et al., 1980). Thereafter, the decline in hemoglobin is reversed as erythropoiesis becomes more active and the level of hemoglobin rises from an average of 11 g/dL to about 12.5 g/dL during the first year of life (Saarinen and Siimes, 1978; Dallman and Siimes, 1979). However, at 4 to 6 months of age and thereafter there is a greater dependence on dietary iron. The rapid rate of growth coupled with the low-iron content of human milk or cow milk may result in the depletion of iron stores. If iron stores are exhausted, the rise in hemoglobin can be curtailed or reversed. The greatest risk of developing iron deficiency occurs between 6

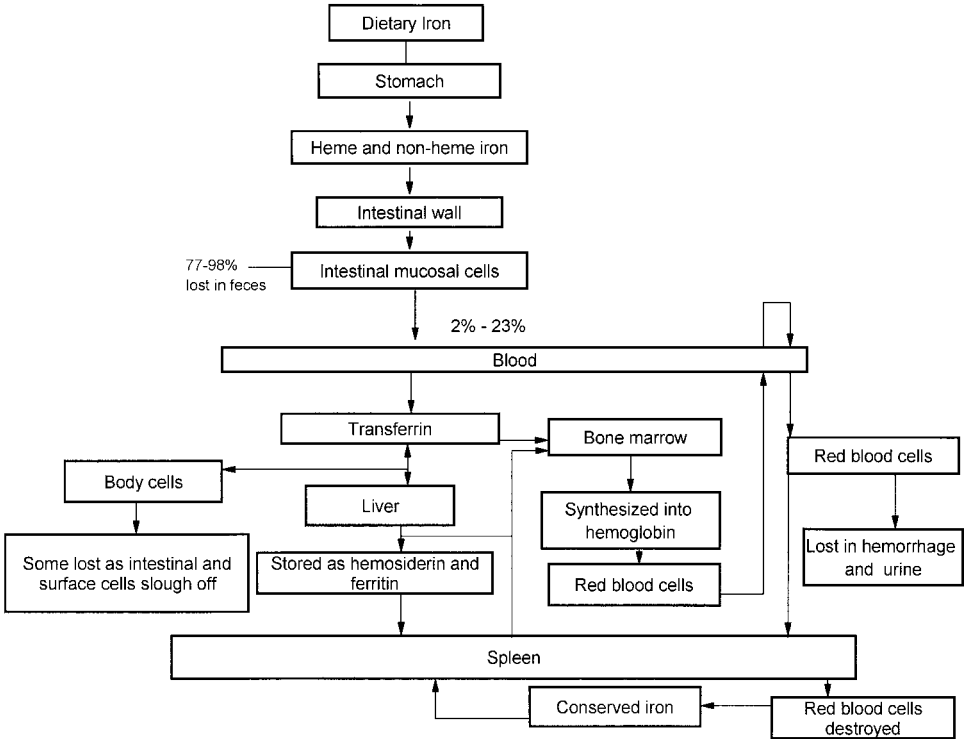

Fig. 1. Process of absorption and metabolism of iron. Many factors influence the absorption of dietary iron. Physiologic needs signal the regulatory mechanisms that increase rate of absorption. Conditions within the intestines and interaction of iron with other nutrients will influence the bioavailability of iron. Redrawn from Guthrie and Picciano (1995).

months and 2 to 3 years of age, when iron stores are likely to become depleted (Dallman et al., 1980).

Iron balance

Total body iron is regulated mainly through the amount of iron absorbed by the intestinal mucosa (Finch and Cook, 1984). Figure 1 illustrates the processes of iron absorption and metabolism. The quantity of body iron is maintained within narrow limits. Often, the amount of iron absorbed is a small fraction of the total amount available in the diet. The degree of iron absorbed is related to the abundance of iron stores, the form and amount of iron in food, and the interaction of foods and/or nutrients that increase or decrease the availability of iron for absorption (Monsen et al., 1978; Fomon, 1993). When the supply of dietary iron is sufficient, the intestinal mucosa regulates iron absorption and tends to keep the body's iron content in equilibrium. During iron deficiency, iron absorption increases (Finch and Cook, 1984). However, the response may not be sufficient to prevent anemia when the amount of iron in the diet is not sufficient. In adults, approximately 95% of the iron required for hemoglobin is recycled from the breakdown of dying red blood cells; only 5% is obtained from dietary sources (Dallman, 1986a). However, due to the rapid expansion of the levels of hemoglobin and myoglobin during the first year of life, infants depend on dietary iron to a greater extent than adults, requiring about 30% of iron from their diet (Dallman, 1986a).

Iron absorption and interactions with other nutrients

Most dietary iron exists in the form of iron salts referred to as non-heme (inorganic) iron. Non-heme iron is obtained from iron in vegetables. Plants contain iron in the form

of metalloproteins, plant ferritins, iron in sap, and iron bound to storage compounds as phytates (Hazell, 1985). A smaller amount of iron is present in the heme proteins, hemoglobin and myoglobin, which are found in meat (Hallberg et al., 1979). Non-heme iron in food is broken down during digestion, partly reduced, and readily absorbed in the ferrous form. The small amount of heme iron that is available in the infant's diet is split from the globin portions of hemoglobin and myoglobin in the intestinal lumen (Dallman et al., 1980). The heme is then absorbed intact by the intestinal mucosa directly into the mucosal cells (Wheby et al., 1970). Studies on adults have shown that heme iron is much more bioavailable than non-heme iron (Hallberg et al., 1979; Hallberg, 1981; Lynch, 1984).

Lynch (1997) has considered in detail the dietary components that influence non-heme iron absorption. While ascorbic acid enhances non-heme iron absorption (Stekel et al., 1986), calcium, certain proteins, phytates, and polyphenols act as inhibitors (Gross, 1968; Merhav et al., 1985; Hallberg et al., 1991; Rossander-Huhen et al., 1991; Brune et al., 1992). Heme iron is generally well absorbed and is not affected by the enhancers or the inhibitors of non-heme iron absorption.

Dietary ascorbic acid directly interacts with non-heme iron in the lumen of the upper small bowel (Lynch, 1997). During digestion, when gastric contents enter the duodenum and the luminal pH rises, ascorbic acid enhances non-heme iron absorption by maintaining iron in a soluble and bioavailable form over a wide pH range (Conrad and Schade, 1968).

Phytates found in cereal foods such as wheat, oats, sorghum, and rice are major inhibitors of iron absorption (Lynch, 1997). Hurrell et al. (1992) and Hallberg et al. (1989) have shown that even small amounts of phytates are strong inhibitors. However, the mechanisms by which phytates inhibit iron absorption are poorly known. Monoferric phytate which is found in bran does not inhibit non-heme iron absorption (Morris and Ellis, 1982), but the formation of diferric and tetraferric phytate complexes in the gut inhibits absorption (Simpson et al., 1981).

Polyphenols are present in tea, in other beverages, and in many vegetables. Disler et al. (1975a, 1975b) have reported that tea is a powerful inhibitor of non-heme iron absorption, primarily because of its tannin content. As in the case of phytates, even small amounts of polyphenols can inhibit absorption. Polyphenols are thought to form complexes between the hydoxyl groups of the polyphenol compounds and iron molecules, causing the iron to be unavailable for absorption.

Animal protein from whole milk, cheese, and egg white diminishes iron absorption, for reasons that are poorly understood (Lynch, 1997). Calcium in milk or as an inorganic salt also greatly reduces non-heme iron absorption. Calcium seems to inhibit non-heme iron absorption by interactions that take place within the intestinal mucosal cells (Hallberg et al., 1992).

Hallberg et al. (1991) demonstrated that the addition of calcium chloride (between 40 mg and 600 mg calcium) caused a dose related reduction (up to 300 mg calcium) in non-heme iron absorption in a meal of wheat rolls containing 3.8 mg of iron and a small amount of inherent calcium (10 mg). When calcium was added to the dough before baking the inhibitory effect was more pronounced. The inhibitory effect was also correlated with an increase in the phytate content of the wheat rolls. It appears that calcium added to the dough reduced phytate degradation during fermentation and baking. Calcium administered at the time the rolls were consumed reduced absorption of non-heme iron directly.

Cook et al. (1991) considered the effects that calcium carbonate, calcium citrate, and calcium phosphate had on non-heme iron absorption in two meals: a high-bioavailable meal containing hamburger and a low-bioavailable meal containing egg, bran flakes, and coffee. The inhibitory effect was greater in the low-bioavailable meal. When taken without food, but with supplements of 18 mg of ferrous sulfate, calcium carbonate did not inhibit absorption of ferrous sulfate. However, calcium citrate and calcium phosphate reduced ferrous sulfate absorption by 49% and 62%, respectively.

Although there is little doubt that many dietary components influence the amount of non-heme iron absorbed, the data are derived from studies analyzing the consumption of single meals by adults. These studies are designed to optimize the identification of the potential enhancing or inhibitory effect of a particular dietary component. In most instances, meals were consumed after an overnight fast. Obviously, this does not represent the usual dietary practices of most individuals who consume a highly varied diet. However, the diets of infants and children are less varied. Thus, it seems plausible that for infants and children there would be close agreement with the results from single meal studies.

The effects of vitamin A and vitamin C deficiency on iron absorption

Nutrition surveys have reported an association between serum retinol levels and hemoglobin concentration in women and children (Mohanram et al., 1977; Suharno et al., 1993; Wolde-Gebriel et al., 1993). The anemia associated with vitamin A deficiency is characterized by a decrease in serum iron concentration, transferrin saturation, total-iron binding capacity, and an increase of storage iron (Hodges et al., 1978). In a study of children 1 to 8 years of age with low serum retinol levels, vitamin A administered for 2 months produced a significant increase in serum retinol levels *and* an increase in hemoglobin, serum iron, and transferrin saturation, but no change in serum ferritin (Mejia and Chew, 1988). Iron alone led to a significant increases in hemoglobin concentration and serum ferritin. These findings suggest that vitamin A deficiency inhibits iron mobilization from iron stores but has little effect on iron absorption. The mechanisms by which vitamin A deficiency inhibits release of storage iron have not been determined.

Individuals who have clinical signs of scurvy or have reduced ascorbic acid stores often show an impairment in the release of iron from reticuloendothelial cells. Administration of ascorbic acid to these individuals produces an increase in serum iron concentration (Wapnick et al., 1970). The factors responsible for the impairment are unknown, but recent in vitro studies by Toth and Bridges (1995) suggest that ascorbic acid plays an important role in modulating ferritin synthesis and iron storage.

During early infancy, there is almost no heme iron in the diet when milk represents the major source of calories. The timing and amount of heme iron added to the diet of infants varies according to the dietary practices of different societies. To ensure optimal iron absorption throughout infancy, it is necessary to select solid foods that can enhance the absorption of iron in the milk feeding.

METHODS OF HEMATOLOGICAL ASSESSMENT

What is iron-deficiency anemia?

The terms iron deficiency and iron-deficiency anemia are sometimes used interchangeably. However, these terms are not synonymous.

The onset of iron-deficiency anemia is usually gradual and is the end result of a series of three sequential stages (Fig. 2). In the first stage (depleted iron stores), the majority of iron needed for hemoglobin synthesis and other metabolic functions must be mobilized from body stores. The result is a depletion of iron stores as indicated by a decline in serum ferritin (Dallman et al., 1980).

In the second stage (iron deficiency without anemia), iron stores are depleted and the amount of iron for transport diminishes. Iron is bound to transferrin and when iron is depleted, transferrin carries fewer iron molecules; hence, it is less saturated. During this stage, a diminished supply of iron to the bone marrow results in iron-deficient erythropoiesis or iron deficiency without anemia (Skikne et al., 1990). Concomitant with a decrease in transferrin saturation is an accumulation of erythrocyte protoporphyrin, a precursor of heme. Hemoglobin levels may or may not decline but there is an increase in the number of microcytic (smaller than normal) cells (Cook and Skikne, 1989). When the serum ferritin is fully depleted, transferrin receptor levels increase (Skikne et al., 1990). Transferrin receptor facilitates the transport of transferrin-bound iron from the extracellular environment to the intracellu-

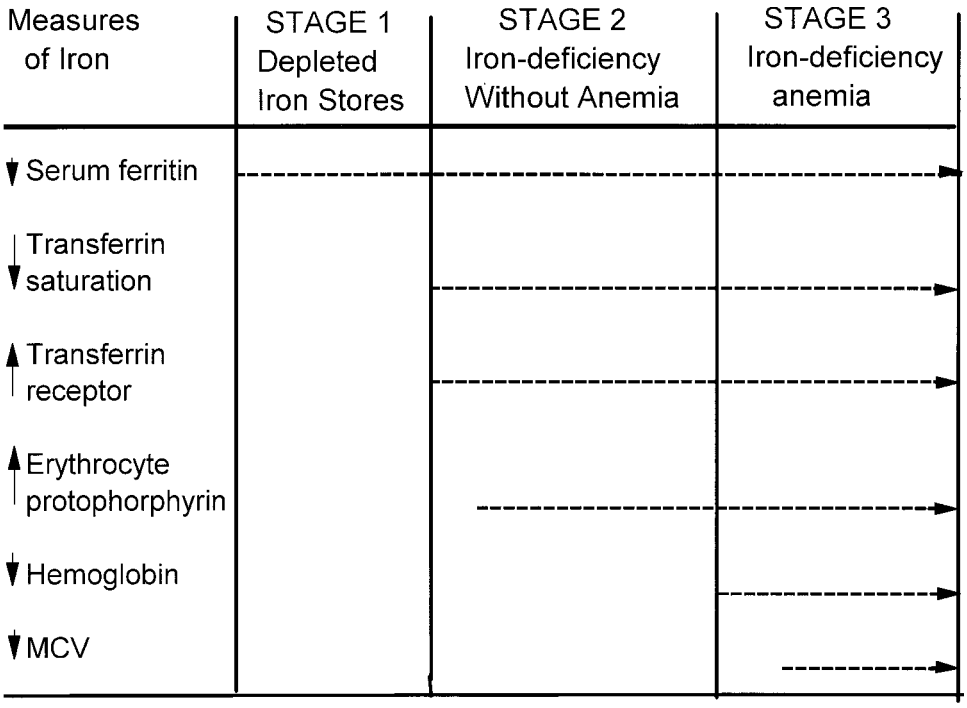

Fig. 2. Progressive development of iron-deficiency anemia. Measures of depleted iron stores, iron deficiency without anemia, and iron-deficiency anemia using multiple biochemical parameters to define the three stages. Note that anemia from infection or chronic disease will cause an increase in serum ferritin.

lar endocytic vesicle and movement of iron to intracellular transport and storage (Baynes et al., 1994). Measurement of transferrin receptor seems to be the most sensitive and reliable index of early tissue iron deficiency; it is also not influenced by chronic infection or inflammation (Cooke and Skikne, 1989).

The third stage (iron-deficiency anemia) involves decreased hemoglobin production. Normal cells are replaced by microcytic cells and hypochromic (less hemoglobin than normal) cells. Iron-deficiency anemia can be identified by a decrease in hemoglobin concentration and/or hematocrit and by a decrease in mean corpuscular volume (MCV) (Shils and Young, 1988).

Iron-deficiency anemia is diagnosed by considering a combination of biochemical indicators of iron status (Looker et al., 1997). A single abnormal value may be misleading; the correlation between individuals having one abnormal value with those with two or more abnormal values has been low (Looker et al., 1997). The laboratory tests most frequently used to define iron deficiency include measures of free erythrocyte protoporphyrin, transferrin saturation, and serum ferritin, although other approaches for estimating iron deficiency have been reported (Cook et al., 1971; World Health Organization, 1978; Leibel et al., 1982; Dallman et al., 1984; Himes et al., 1997). The presence of iron deficiency is determined if an individual has abnormal iron status by two or three tests. This approach has been taken by the National Center for Health Statistics (NCHS) in NHANES II (Pilch and Senti, 1984; Expert Scientific Working Group, 1985) and in NHANES III (Looker et al., 1997). Iron-deficiency anemia is defined as having iron deficiency *and* a low hemoglobin value. The cutoff values for free erythrocyte protoporphyrin, transferrin saturation, serum ferritin, and hemoglobin used by NCHS are shown in Tables 1 and 2. Details of the blood collection procedures and assay methods for

TABLE 1. NHANES III (1988–1994) cutoff values for laboratory tests of iron status[1]

Age (years)	Transferrin saturation (%)	Serum ferritin (μg/L)	Erythrocyte protoporphyrin (μmol/L RBCs)
1–2	<10	<10	>1.42[2]
3–5	<12	<10	>1.24[3]
6–11	<14	<12	>1.24
12–15	<14	<12	>1.24
≥16	<15	<12	>1.24

[1] Data from Looker et al. (1997).
[2] 80 μg/dL of red blood cells (RBCs).
[3] 70 μg/dL RBCs.

TABLE 2. NHANES III (1988–1994) hemoglobin cutoff values

Age (years)	Cutoff value, g/dL[1–3]
Both sexes	
1–2	<11.0
3–5	<11.2
6–11	<11.8
Female	
12–15	<11.9
16–19	<12.0
20–49	<12.0
50–69	<12.0
≥70	<11.8
Male	
12–15	<12.6
16–19	<13.6
20–49	<13.7
50–69	<13.3
≥70	<12.4

[1] Individuals with abnormal or missing values for transferrin saturation, erythrocyte. protophorphyrin, serum ferritin, or mean corpuscular volume were excluded.
[2] Defined as mean hemoglobin − 1.645 standard deviation.
[3] Data from Looker et al. (1997).

the biochemical measures of iron status have been described by Gunter et al. (1996) and Looker et al. (1995). A description of the serum receptor assays used to measure transferrin receptor levels is also available (Kohgo et al., 1987; Flowers et al., 1989). Cutoff values for transferrin receptor have not yet been determined for specific age and gender subgroups. However, a transferrin receptor level >9 mg/dL has been used as a measure of iron deficiency in adults (Cook and Skikne, 1989).

It is important to note that the methods used by NCHS to diagnose iron-deficiency anemia have some limitations. Transferrin saturation and erythrocyte protoporphyrin cannot distinguish between iron-deficiency anemia and the anemia that is associated with infection, inflammation, or chronic disease (Cook and Skikne, 1989; Ferguson et al., 1992; Cook et al., 1993). An elevation of serum ferritin, independent of an individual's iron stores, is associated with liver disease, chronic infection, and alcohol abuse (Cook et al., 1993). Furthermore, blacks tend to have smaller red blood cell masses than nonblacks and their hemoglobin concentration averages about 1 g/dL lower than nonblacks (Owen et al., 1973; Garn et al., 1975, 1981a, 1981b; Meyers et al., 1979; Cresanta et al., 1987; Perry et al., 1992; Himes et al., 1997). Thus, the NCHS cutoff values for hemoglobin may over estimate the prevalence of iron-deficiency anemia in blacks. Some researchers have pointed out the need for population-specific cutoff values for hemoglobin concentration (Dallman et al., 1978; Johnson-Spear and Yip, 1994).

Several studies have shown that the hemoglobin and hematocrit differences between black and white groups are evident even when socioeconomic factors and iron status (serum ferritin and erythrocyte protoporphyrin) are controlled (Garn et al., 1975, 1981a, 1981b; Dallman et al., 1978; Yip et al., 1984). The most likely explanation for the lower biochemical values observed in blacks is the presence of mild thalassemias (α-thalassemia trait and β-thalassemia trait) that limit hemoglobin production and are known to cause anemia. For this reason, using uniform cutoff values to diagnose iron-deficiency anemia would provide the opportunity to detect not only nutritional anemia but some of the hereditary hemoglobinopathies as well (Yip et al., 1984). In black infants and children who are found to have anemia, factors other than iron deficiency should be considered, particularly if there is no improvement in hemoglobin concentration after iron therapy (Yip et al., 1984).

PREVALENCE OF IRON DEFICIENCY AND IRON-DEFICIENCY ANEMIA

Although the prevalence of iron-deficiency anemia in the United States is now relatively low (Table 3), it is still a major problem in certain segments of the infant population. Data from the Pediatric Nutrition Surveillance System (PNSS), conducted by the Centers for Disease Control (CDC) in 1980–1991, indicated a 20–30% overall prevalence of anemia among children youn-

TABLE 3. Prevalence of iron deficiency and iron-deficiency anemia in the United States, NHANES III 1988–1994

Age (years)	N	Iron deficiency (%)	Iron-deficiency anemia (%)
Both sexes			
1–2	1,339	9	3[1]
3–5	2,334	3	<1
6–11	2,813	2	<1
Females			
12–15	786	9	2[1]
16–19	700	11[1]	3[1]
20–49	4,495	11	5[1]
50–69	2,034	5	2
≥70	1,630	7[1]	2[1]
Males			
12–15	691	1	<1
16–19	658	<1	<1
20–49	4,048	<1	<1
50–69	1,929	2	1
≥70	1,437	4	2

Data from Looker et al. (1997).
[1] Prevalence in nonblacks is 1% lower than prevalence in all other groups.

ger than 2 years of age (Yip et al., 1992) (Fig. 3). The PNSS monitors the nutritional status of low-income children in the United States who are enrolled in public health programs such as the Women, Infants, and Children supplemental food program (WIC). Hemoglobin and hematocrit measurements were used to diagnose anemia. The CDC criterion for anemia for children younger than 2 years of age was a hemoglobin <11.0 g/dL or a hematocrit of <33%. Black children had a consistently higher prevalence of anemia (>20%) than other groups (Fig. 3). One likely explanation for the high rates of anemia among children in the PNSS is the preference given to anemic children for participation in the WIC program.

The prevalence of anemia is particularly high among Alaskan Native children (Thiele et al., 1988). Hemoglobin and hematocrit values from the Alaska Area Native Health Service Survey, conducted in 1983–1985, indicated that the prevalence of anemia (hemoglobin <11.0 g/dL, hematocrit <34%) ranged from 22% to 28% in children under 5 years of age. The high level of anemia observed in these groups is of concern and suggests that many of these children had poor iron nutrition even though they participated in WIC. One possible reason for the reported high level of anemia is poor compliance to the WIC program. More information is needed to determine the extent to which children consumed the iron-fortified foods provided by WIC.

Canada does not have a food supplemental program such as WIC and intake of whole cow milk by older infants is common. A survey conducted in 1989–1990 assessed the prevalence of iron-deficiency anemia in 1-year-old children (10 to 14 months of age) from disadvantaged families in Montreal (Lehmann et al., 1992). A disadvantaged family was defined as one in which the mother had not finished high school and the family income was below the "poverty level" as defined by the Canadian government ($19,633 for a family of three). Iron-deficiency anemia was defined as a serum ferritin level <10 μg/L and either a hemoglobin <11.5 g/dL or an MCV of <72 fL. Iron-deficiency anemia was found in 25% of the children surveyed. The authors suggested that the use of whole cow milk before 6 months of age and the use of iron-fortified cereal for less than 6 months were significant predictors of developing iron-deficiency anemia (Lehmann et al., 1992).

The prevalence of iron deficiency was determined in a population of Chinese children 6 to 36 months of age living in Montreal (Chan-Yip and Gray-Donald, 1987). Of the 346 children studied, 12.1% were found to be iron deficient. Children with at least one abnormal iron value (i.e., low serum iron, elevated free erythrocyte protoporphyrin, or elevated total iron-binding capacity) were treated with ferrous sulfate for 3 months. Those who responded to therapy with a rise in hemoglobin level of at least 1 g/dL were identified as iron deficient. Cases of mild iron deficiency without anemia were not identified because determination of ferritin levels was not made. More infants 6 to 12 months of age who were breast-fed for at least 2 months than who were bottle-fed were iron deficient (27.0% vs. 7.0%). Many of the infants in the study were fed traditional Chinese food, which is known to have low iron bioavailability (Hsia and Yeung, 1976). This study demonstrated that the combination of human milk and traditional foods with low amounts of iron may have led to a higher prevalence of iron deficiency than expected.

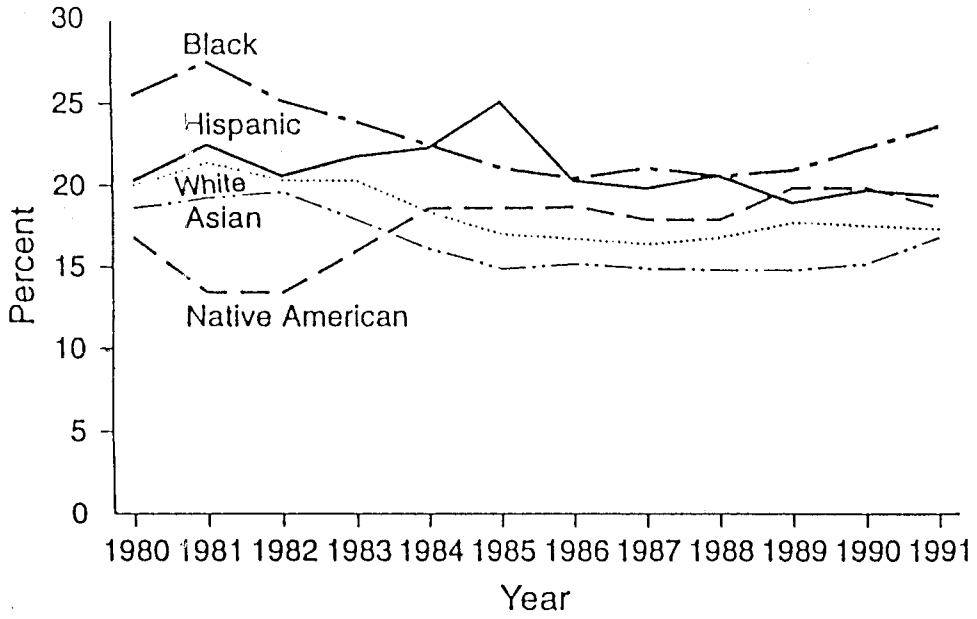

Fig. 3. Trends in prevalence of anemia among low-income children <2 years of age, United States, 1980–1991. Data from the Pediatric Nutrition Surveillance System (PNSS) (Yip et al., 1992). The criterion for anemia is a hemoglobin <11.0 g/dL or a hematocrit of <33%. Since 1980, the prevalence of anemia has declined, but black children had a consistently higher prevalence of anemia than did all the other groups. The overall prevalence of anemia (20–30%) in low-income children included in the PNSS was much higher than the 3% national prevalence (see Table 3).

The prevalences of iron deficiency (ferritin ≤10 μg/L) and iron-deficiency anemia (hemoglobin ≤11 g/dL plus either a ferritin concentration of ≤10 μg/L or a free erythrocyte protoporphyrin >99 μg/L) were estimated in 428 randomly chosen infants and toddlers aged 8 to 15 months living in four Canadian cities (Toronto, Montreal, Edmonton, and Halifax) (Zlotkin et al., 1996). The socioeconomic status of the sample reflected the general population in the four cities, but the educational training of the parents was higher than the general population. There were no significant differences in the prevalence of iron deficiency and iron-deficiency anemia among the four cities. Only 4.3% of the population had iron-deficiency anemia, but 33.9% had iron deficiency. Exclusive breast-feeding was practiced by 76.9% of mothers for an average of 5.2 months. Infants who were breast-fed exclusively or fed iron-fortified formula had mean ferritin levels significantly higher than infants fed cow, soy, goat, or evaporated milk.

The iron status and feeding practices of 434 infants living in Vancouver were determined at 38 to 40 weeks of age (Innis et al., 1997). The infants were from middle-to-high-income families with parents who had completed some post-secondary education. Iron-deficiency anemia was defined as having a low hemoglobin (≤10.1 g/dL) or a low hemoglobin value (≤11.0 g/dL) with two or three abnormal results from tests of serum ferritin (≤10 μg/L), zinc erythrocyte protoporphyrin (>70 μmol/mol heme), and total iron binding capacity (>60 μmol/L). Infants without iron-deficiency anemia with a serum ferritin of ≤10 μg/L were considered to be iron deficient. Approximately 7% of the infants examined had iron-deficiency anemia and about 24% were iron deficient. Iron-deficiency anemia occurred more frequently among infants who were breast-fed for more than 3 months. The prevalence of iron-deficiency anemia among infants breast-fed to 9 months of age was 15%. Low iron stores were also more common among infants who

were given cow milk, a low-iron formula, or who were breast-fed regardless of breast-feeding duration. Failure to introduce iron-fortified infant cereals was not related to iron status in any group. However, data on the amount and kinds of solid food consumed were not quantified. It is possible that the amount of iron-fortified foods administered to breast-fed infants was insufficient to meet their iron needs.

Over the past two decades, consensus has been reached for the prevention of iron-deficiency anemia by promoting breast-feeding, using iron-fortified infant formula for breast-fed infants when they are weaned, using iron-fortified formula for those infants who are not breast-fed, using iron-fortified infant solid foods during the second 6 months of life for all infants, and delaying the use of cow milk until the second year of life (American Academy of Pediatrics, 1976, 1989; Fomon, 1987; Dallman, 1988). The relatively high rates of iron-deficiency anemia observed in different infant populations appear to be associated with the early introduction of cow milk, prolonged breast-feeding and/or feeding solid foods with low bioavailable iron. Many of the studies mentioned above, however, did not consider the amount and kinds of solid foods consumed; many foods in the diet may have compromised the bioavailability of iron. It still remains unclear why some infants remain iron sufficient longer than others regardless of the kinds of milk and foods consumed.

IRON STATUS AT BIRTH AND REQUIREMENTS DURING INFANCY

Maternal iron status during pregnancy and infant iron stores at birth

It is generally believed that the fetus obtains and stores its required amount of iron even when the mother is iron deficient. However, this assumption may not be true. Although the extent to which maternal iron deficiency affects infant iron stores has not been clearly determined, poor iron status during pregnancy may have significant consequences on neonatal health.

Major changes in iron metabolism occur during pregnancy. Menses temporarily ends, red blood cell mass expands by approximately 20%, and iron is deposited in the fetus and placenta (Allen, 1997). Most of the fetal iron is obtained after 30 weeks of gestation, when the maternal serum ferritin levels are constant. In response to estrogenic hormones, circulating maternal serum transferrin increases by about 250% (Allen, 1997).

Fetal iron is obtained from maternal transferrin which delivers iron to transferrin receptors on the placenta. The amount of iron transferred across the placenta depends on the number of transferrin receptors on the maternal side and the concentration of ferritin in the cells (Allen, 1997). To help maintain a constant flow of iron at appropriate levels, the number of transferrin receptors increases if cellular iron is low and decreases if cellular iron is high.

During the first trimester of pregnancy, iron requirements are lower because of the cessation of menses. The need for iron increases at around 16 weeks of gestation when maternal blood volume and red cell mass expand. The total amount of iron required for an average pregnancy is 840 mg, of which 350 mg is transferred to the fetus and placenta, 250 mg is lost in blood at delivery, and 240 mg is basal losses (Institute of Medicine, 1990). When women are supplemented with iron during pregnancy, at 2 months postpartum their iron stores may be higher than before they conceived (Svanberg et al., 1976). Among women who became iron deficient during pregnancy, their iron stores remain depleted in the first few postpartum months (Puolakka et al., 1980; Milman et al., 1991).

An in-depth and critical review of the literature on the relationship between maternal iron deficiency and neonatal health has been presented by Allen (1997). Most of the literature supports the view that the fetus obtains required amounts of iron regardless of its mother's iron status. However, these studies have considered the relationship between iron status in late pregnancy and iron indices in cord blood in women who were not iron deficient or who were given iron supplements late in pregnancy (Rios et al., 1975b; Ajayi, 1988; Doyle et al., 1990). In studies where anemia is present, cord blood iron measures have been found to be closely associated with maternal concentrations. For

example, in Nigeria, mothers with low iron stores (serum ferritin <20 μg/L) at term had significantly lower cord serum ferritin levels (88 μg/L) than women with adequate stores (150 μg/L) (Ajayi, 1988). In a study where pregnant Dutch women were given 66 mg of iron or a placebo daily from 16 weeks gestation to term, newborn infants had higher cord serum ferritin concentrations than the placebo group (155 μg/L vs. 118 μg/L) (Milman et al., 1991). Iron deficiency (cord ferritin <80 μg/L) occurred in 5% of the treated group and 26% in the placebo group (Milman et al., 1991).

Many studies on the relationship between maternal and infant iron stores end at birth and do not consider the older infant. A stronger association appears to occur after 4 to 6 months when the infant's iron stores are depleted. A long-term prospective study of 156 mothers and infants was conducted to evaluate the relationship between iron-deficiency anemia during pregnancy (hemoglobin <11.0 g/dL and ferritin <12 μg/L at birth) and the development of iron-deficiency anemia during infancy (hemoglobin <11.0 g/dL and ferritin <12 μg/L) (Colomer et al., 1990). Infants of anemic mothers were more likely to become anemic by 12 months of age (odds ratio = 6.57) even after controlling for several confounding variables including socioeconomic status, feeding practices, and morbidity.

Iron-deficiency anemia is the most common nutritional disorder during pregnancy, affecting an average of 56% pregnant women in developing countries and 18% in developed countries (World Health Organization, 1992). The prevalence of iron deficiency which precedes iron-deficiency anemia is even higher. Further research is needed to better understand the potential detrimental effects on maternal and infant health caused by iron-deficiency anemia during pregnancy.

Dietary requirements during infancy

Infants must obtain most of the iron they need for growth and maintenance from dietary sources (Crichton and Ward, 1992). Human milk contains approximately 0.5 mg of iron per liter during early lactation and about 0.35 mg per liter thereafter (Lonnerdal, 1990). The iron concentration of colostrum is somewhat higher. The amount of iron in human milk *is not* associated with the mother's iron nutritional status (Fomon, 1993). Most of the iron in human milk is found in the fat globule membranes of the lipid fraction, in the low-molecular-weight fractions, and in lactoferrin (Fransson and Lonnerdal, 1980; Lonnerdal, 1990). Approximately 30% of iron in human milk is in lactoferrin (Lonnerdal, 1990; Fransson and Lonnerdal, 1980).

Cow milk has the same concentration of iron as human milk, but the bioavailability of iron from human milk is believed to be relatively high, about 50% (Schulz-Lell et al., 1987) on the average. In contrast, only 10% of the iron in cow milk is absorbed. The reasons for the high bioavailability of iron in human milk are unclear. However, the high concentration of calcium and protein and the low concentration of ascorbic acid are responsible for the poor absorption of iron from cow milk (see above). The consensus among researchers (Cook and Brothwell, 1984; Lonnerdal, 1984; Lynch, 1984; Lonnerdal, 1989) that approximately 50% of the iron in human milk is absorbed is based on studies that measure the absorption of lactoferrin. However, the amount of iron absorbed from all the components of human milk iron has not been determined (Fomon, 1993).

The iron requirement during the first year of life is based on the amount needed for the desired increment in total body iron plus the amount needed to replace inevitable losses (Stekel, 1984; Fomon, 1993). Fomon (1993) calculated iron requirements for two hypothetical infants: one with a birth weight of 3.5 kg and weight of 10.5 kg at 1 year of age, and the other with a birth weight of 2.5 kg and weight of 10.0 kg at 1 year. The sum of the desired increment in total body iron plus the quantity needed to replace iron losses is 200 mg for the hypothetical infant with a birth weight of 3.5 kg and 270 mg for the hypothetical infant with a birth weight of 2.5 kg (Fomon, 1993) (Table 4). These estimates divided by 365 days indicate that the daily requirements of iron are 0.55 and 0.75 mg/d, respectively. Similar estimates have been provided by Stekel (1984).

These estimates are consistent with observations that infants fed iron-fortified infant formula providing approximately 12 mg of iron per liter usually remain in satisfactory

TABLE 4. Estimated requirement for absorbed iron in infancy

	Requirement for absorbed iron during the first year of life (mg)[1]			
	3.5 kg at birth, 10.5 kg at 1 year		2.5 kg at birth, 10.0 kg at 1 year	
Hemoglobin	27		260	
Myoglobin and enzymes	54		52	
Storage	53		56	
Body iron at 1 year	377		362	
Body iron at birth	268		183	
Increment in total body iron (Body iron at 1 year–body iron at birth)		109		179
Losses of iron				
Gastrointestinal	69		62	
Dermal	29		29	
Total losses		91		91
Total		200 (0.55 mg/d)		270 (0.75 mg/d)

[1] Data from Fomon (1993: Table 14-5).

iron nutritional status (Hertrampf et al., 1986; Pizarro et al., 1991). The iron intake of an infant who consumes 830 ml/d of a formula providing 12 mg of iron per liter is 10 mg/d. When healthy infants are fed milk-based or soy protein-based formulas providing 12 mg of iron (label claim) and 60 mg of ascorbic acid (label claim), the mean absorption of iron is 4% to 5% (Rios et al., 1975a). With these absorption rates, infants will absorb 0.40 to 0.50 mg of iron per day. Some iron will also be provided from other foods in the infant's diet.

Recently, Fomon and his associates (1997) considered iron absorption in infants fed formulas with an iron concentration of 12 mg/L or 8 mg/L. Infants entered the study at 112 days of age and were examined at 196 days of age. Using the stable isotope of iron (^{58}Fe), erythrocyte incorporation of iron was measured. The difference in the amount of ^{58}Fe incorporated into erythrocytes by infants fed formula with an iron concentration of 12 mg/L was not significantly different from that of infants fed formula with 8 mg iron/L. Because iron absorption was not greater among infants fed formula with 12 mg iron/L than those fed 8 mg iron/L, the authors suggested that the iron concentration of iron-fortified infant formulas can be decreased. However, it is important to note that infants were in good iron nutritional status before and after the end of the study. Before study entry, infants received iron-fortified formula (12 mg/L) or iron supplements. Beginning at 140 days of age, solid foods were permitted (strained pears) and after 161 days of age other food items were permitted. It is not known whether feeding a formula with 8 mg iron/L beyond 196 days of age would prevent iron deficiency later in life. It is also unclear whether a lower level of iron would be efficacious in the general population of infants where there is variation in the timing and types of solid foods introduced into the diet.

TABLE 5. Iron absorption from human milk

Age (weeks)	Quantity of milk consumed (L)	Iron		
		Concentration (mg/L)	Consumed (mg)	Absorbed (mg)[1]
0–6	0.85	0.50	0.42	0.21
6–26	0.85	0.35	0.29	0.15

[1] Assumes 50% absorption.

Even though absorption from human milk is approximately 50%, the level of iron in human milk is too low to meet the iron needs of infants. For example, if an infant consumes 850 ml of human milk per day during early infancy when the iron concentration is 0.5 mg/L and then consumes 850 ml in late infancy when the iron concentration is 0.35 mg/L, the amount of iron ingested would be 0.42 and 0.29 mg/d, respectively (Table 5). If 50% of the iron is absorbed, the amount absorbed would be approximately 0.15 to 0.21 mg of iron per day, amounts much lower than the estimated requirements of 0.55 to 0.75 mg/d.

Iron requirement for breast-fed infants

Although breast-fed infants can maintain adequate iron stores for 4 to 6 months (Saarinen et al., 1977; Saarinen, 1978; Duncan et al., 1985), there is strong evidence

that supplemental iron is needed thereafter. The most convincing evidence is provided by Pizarro et al. (1991). The iron status of 854 9-month-old infants on three different feeding regimens and on a regimen that included an iron-dextran injection was considered in a prospective, randomized clinical trial. All infants were enrolled during three field trials conducted in Santiago, Chile, from 1975 to 1985. Infants in the breast-fed group were breast-fed for at least 9 months. Infants in the formula groups were partially or totally weaned to formula before the age of 6 months and randomly received either a non-iron-fortified formula or an iron-fortified formula. A group of breast-fed infants were injected intramuscularly with 150 mg of iron-dextran on the second or third day of age and were fed non-iron-fortified infant formula after being weaned. All infants with a hemoglobin concentration of $<$11.0 g/dL were classified as having anemia. Infants who had two or three abnormal biochemical measures (erythrocyte protoporphyrin $>$120 μg/dL, transferrin saturation $<$10%, and serum ferritin $<$10 μg/L) were classified as having iron-deficiency anemia. Fruit was introduced into the diet of all infants at 3 months of age, a meat-and-vegetable soup at 4 months, legumes and eggs at 6 months, and table food at 9 months. The solid foods were not iron fortified.

The prevalence of iron deficiency was highest in the group of infants fed non-iron-fortified formula (37.5%), intermediate in the group fed human milk (26.5%), much lower in the group fed iron-fortified formula (8.0%), and absent from the group injected with iron-dextran. The corresponding values for iron-deficiency anemia were 20.2%, 14.7%, 0.6%, and 0%, respectively. As compared with a non-fortified infant formula, human milk, despite its low iron content, provided greater protection against iron-deficiency anemia (Saarinen, 1978; Siimes et al., 1984; Pizarro et al., 1991). However, breast-feeding as the exclusive source of milk for 9 months was associated with a relatively high prevalence of iron deficiency and iron-deficiency anemia. For this reason, there is general agreement that breast-fed infants receive additional bioavailable sources of iron starting by 6 months of age (American Academy of Pediatrics, 1976; Pizarro et al., 1991).

Requirement of iron for low-birth-weight infants

Of special concern is the requirement of iron in low-birth-weight infants. In 1993, 11% of all births in the United States were preterm; the rate of low birth-weight was 7.2% (Ventura et al., 1995). In the same year, the rate of preterm births to blacks was 18.5% and the prevalence of low birth-weight was 13.3% (Ventura et al., 1995).

In low-birth-weight infants, the total body iron is lower than in full-term infants, although the proportion of iron to body weight is similar (Oski, 1993). Low-birth-weight infants may show a faster rate of postnatal growth than full-term infants (Hack et al., 1996), and unless the diet is supplemented with iron, they become iron depleted more rapidly. In low-birth-weight infants, iron deficiency can develop at 2 to 3 months of age (Oski, 1993). The American Academy of Pediatrics (1977) does not recommend iron supplementation before 1 to 2 months even though body stores may be depleted because low-birth-weight infants may develop hemolytic anemia in the presence of vitamin E deficiency (Melhorn and Gross, 1971). However, recent data have not demonstrated an adverse effect of iron supplementation since formulas have been changed to maintain a vitamin E:polyunsaturated fatty acid ratio of greater than 1 (Zipursky et al., 1987).

Ziegler et al. (1981) and Lundstrom et al. (1977) have suggested that oral supplements should be administered at about 2 weeks of age, or when enteral feedings are tolerated, at a dose of 2 to 3 mg/kg/d. If iron is administered this early, vitamin E supplements should be given as well. A higher daily dosage of iron for very-low-birth-weight infants is necessary (Siimes, 1982). This recommended regimen should start by 2 months of age and continue to 12 to 15 months of age: birth-weight, 1,500 to 2,000 g, 2 mg/kg/d; birth-weight 1,000 to 1,500 g, 3 mg/kg/d; birth-weight less than 1,000 g, 4 mg/kg/d.

IRON IN THE DIET OF INFANTS

Iron deficiency during infancy and early childhood results when the diet does not

supply the estimated requirement of 0.55 to 0.75 mg of iron per day (Fomon, 1993). Although iron in human milk is well absorbed, a low amount is available. Unfortunately, many foods commonly fed to infants in developing and industrialized countries are also low in iron. Therefore, much of the iron in the infant's diet, particularly in industrialized countries, is obtained from the iron added to commercially available infant foods such as iron-fortified infant formula, infant cereals, cereal-fruit products, and grape juice (Fomon et al., 1989).

Infant cereals

When infant cereals were introduced into the United States, they were fortified with sodium iron pyrophosphate (Schultz and Smith, 1959). Schultz and Smith (1958) indicated that this form of iron was well absorbed by infants. However, subsequent studies by Rios et al. (1975a) demonstrated otherwise. Rios et al. (1975a) reported the geometric mean absorption of iron by infants fed cereals with various forms of iron. The geometric mean absorption was only 1.0% for sodium iron pyrophosphate; the mean absorption rate was 4% for electrolytic iron powder. The electrolytic iron powder was of smaller particle size than other iron products being used at the time. Presently, infant cereal is fortified with electrolytic iron powder at the level of 45 mg/100 g of dry cereal. For many years, the commercially used electrolytic iron was believed to be well absorbed. However, several recent studies have suggested that the bioavailability of electrolytic iron may be lower than originally thought (Hurrell, 1984; Fomon, 1987).

Walter et al. (1993) compared iron-fortified rice cereal with non-fortified rice cereal fed to 512 infants in Chile. The iron-fortified rice cereal contained 55 mg of electrolytic iron per 100 g of dry cereal. A group of infants who were weaned from the breast early were randomized into three feeding groups: fortified cereal with non-fortified formula, non-fortified cereal with non-fortified formula, and non-fortified cereal with fortified formula. Measurements of iron status were obtained at 8, 12, and 15 months of age. Infants with hemoglobin values <10.5 g/dl were considered anemic. Walter and his colleagues (1993) reported that among infants weaned early to formula, 8% of infants in the fortified cereal + non-fortified formula group, 24% of infants in the non-fortified cereal + non-fortified formula group, and 4% of infants in the non-fortified cereal + fortified formula group had anemia. The authors suggested that iron-fortified infant rice cereal contributed substantially to preventing iron-deficiency anemia. However, the bioavailability of the iron was enhanced by the ascorbic acid in the infant formulas. In a study where cow milk was substituted for infant formula, it was shown that infants were at a risk of developing depleted iron stores, even though the intakes of iron from infant cereal and ascorbic acid from juices were above the recommended dietary allowance (RDA) (Fuchs et al., 1993). The authors suggested that iron insufficiency was not the result of inadequate intakes of iron or ascorbic acid but probably due to the relatively poor bioavailability of iron in infant cereal (Fuchs et al., 1993). The high calcium levels in cow milk may have also inhibited the absorption of iron from cereal.

Infant formulas and iron-fortified foods

Both iron-fortified milk-based (Hertrampf et al., 1986; Pizarro et al., 1991) and soy protein-based formulas (Hertrampf et al., 1986) are effective in preventing iron deficiency and contain a sufficient amount of iron in the form of ferrous sulfate. Commercially available cereal-fruit mixtures fortified with ferrous sulfate are also good sources of bioavailable iron (Fomon et al., 1990). Most strained meats contain 0.9 to 1.5 mg of iron/100 g in the form of heme iron (Gerber Products Company, 1992). Egg yolk also provides ample amounts of iron, containing approximately 2 mg of iron/100 g. However, egg yolk contains phosphoprotein which binds with iron and decreases its bioavailability (Lynch, 1984).

Infant feeding practices

National surveys of food intake by older infants (6.5–13.4 months of age) have described the relationship between the milk feeding in the infant's diet and nutrient intakes, including iron (Martinez et al., 1985; Montalto et al., 1985; Martinez and Ryan,

TABLE 6. Median iron intakes of infants fed iron-fortified formula or cow milk[1,2]

Age (months)	Iron-fortified formula N	Iron-fortified formula Iron intake (mg/d)	Cow milk N	Cow milk Iron intake (mg/d)
6.5–8.4	95	19.2	54	11.4
8.5–10.4	135	17.4	144	9.6
10.5–12.4	82	23.1	170	9.2

[1] Data from Martinez et al. (1985).
[2] Breast-fed infants excluded. Iron-fortified formula contains 12 mg/L and cow milk contains 0.5 mg/L or iron.

1985; Ryan and Martinez, 1985; Ernst et al., 1990). These surveys indicated that infants who received an iron-fortified infant formula had median intakes of iron that exceeded the 1980 (15 mg/d) and 1989 (10 mg/d) RDAs (Table 6). The median intake of iron by infants on a diet that included cow milk was below the 1980 RDA but at or slightly above the more recent 1989 RDA (Table 6). Infants who were fed a diet that included iron-fortified formula received over 80% of their iron from two sources—infant cereal and iron-fortified formula. These two sources combined provided amounts of iron that exceeded the 1980 or 1989 RDA.

Solid food and infant cereal represented the major sources of iron for infants fed cow milk (more than 95%) (Martinez et al., 1985). Infant cereal alone provided 50–60% of the iron intake (Martinez et al., 1985). However, these foods combined did not provide a sufficient amount of iron to exceed the 1989 RDA.

These surveys indicated that medicinal iron in the form of vitamin preparations were used by a low percentage of infants fed cow milk (22–44%) (Martinez et al., 1985). In practice, supplements are typically not reliable because of poor compliance (Martinez et al., 1985); they also present a risk of toxicity to both infants and siblings (Dallman, 1986b).

The reported decline in the prevalence of anemia in the United States from the 1960s through the 1980s has been attributed to a generalized improvement of iron nutrition in infancy and childhood (Miller et al., 1985; Vasquez-Seoane et al., 1985; Yip et al., 1987a, 1987b; Yip, 1989). During this time period, there were substantial increases in the use of iron-fortified infant formulas and human milk (Ryan et al., 1990) (Fig. 4); these increases have been primarily at the expense of whole cow's milk and low-fat milk (Ryan et al., 1990). Recent surveys of breast-feeding practices in the United States have indicated a resurgence in the prevalence of the initiation of breast-feeding and the persistence of breast-feeding to 6 months of age (Ryan, 1997). The increases of breast-feeding were observed across all socioeconomic groups but were more marked among groups that have historically been least likely to breast-feed: women who are black, receiving WIC benefits, less than college educated, primiparous, employed full-time, and living in regions of the country where mothers are less inclined to practice breast-feeding (East South Central, West South Central, Middle Atlantic, and South Atlantic). Despite the increased use of human milk and iron-fortified formula, iron-deficiency anemia is still a major problem in some infant populations (see above).

IRON-DEFICIENCY ANEMIA AND GROWTH

Impaired growth among anemic children has been attributed to several factors including anorexia, alterations in regulation of growth hormone, and decreased intestinal function (Lawless et al., 1964; Naiman et al., 1964; Harris and Kellermeyer, 1970; Oski, 1979; Donnadieu et al., 1980). Animal studies with rats have demonstrated that moderate to severe iron-deficiency anemia is associated with reduced food intake and marked growth retardation (McCall et al., 1962; Dallman, 1969). Retardation and cessation of fetal development have been reported in pregnant rats with maternal iron deficiency (Finch et al., 1983). Carefully controlled pair-fed rat studies have shown that iron deficiency, independent of anorexia, decreases growth by negatively affecting cell division in growing organs (Canale and Lanzkowsky, 1970). Humans with anemia often complain of temporary anorexia (Lawless et al., 1994). Infants and adults with iron deficiency have been reported to show an increase in appetite 3 to 5 days after iron therapy (Harris and Kellermeyer, 1970; Lawless et al., 1994).

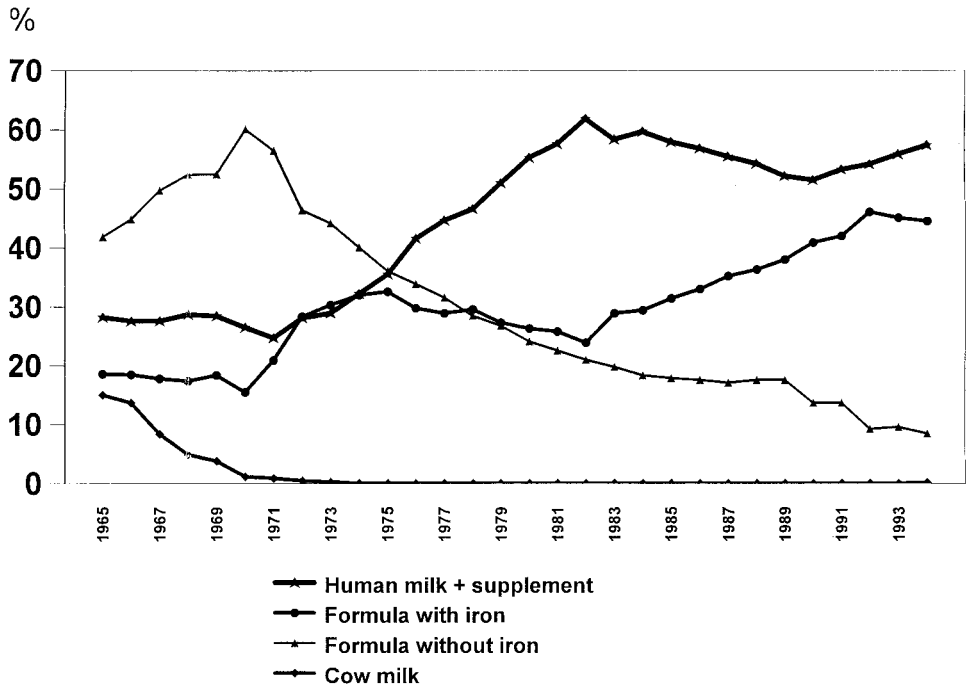

Fig. 4. Infant feeding trends in the United States, 1965–1996, in hospital. Between 1965 and 1996, there was a greater than twofold increase in the frequency of breastfeeding in the hospital (28% to 59%). Between 1984 and 1989 there was a short-term decline in the initiation of breastfeeding (from 59% in 1984 to 52% in 1989). This decline was completely reversed during 1989 to 1996. Concomitant with the long-term increase in breast-feeding was an increase in the use of iron-fortified infant formula. During the same period, the use of non-iron-fortified formula decreased substantially.

Regulation of growth hormone secretion is related to variations in serum transferrin levels; gains in height and weight are positively related to higher serum transferrin levels in children (Donnadieu et al., 1980). It is unclear whether transferrin directly acts on growth hormone secretion or on a cofactor.

Naiman et al. (1964) have shown decreases in small intestinal absorption of fat in infants with iron-deficiency anemia. Other iron compounds that are adversely affected when iron-deficiency anemia develops include heme iron, iron sulfur, metalloflavoproteins, and enzymes that do not contain iron but require it as a cofactor. These factors play an important role in rate of tissue growth, oxidative metabolism, and tissue workload.

When considering the literature on the relationship between iron-deficiency anemia and growth, it is difficult to determine at what point an infant's diet becomes sufficiently deficient to impair growth. It is also unclear whether iron-deficiency anemia alone is associated with slower growth because iron-deficiency anemia may coexist with other nutritional deficiencies. Further, many studies were not designed specifically to evaluate the effects of iron-deficiency anemia on growth. Rather, the primary purpose was to determine whether iron therapy could reverse slower rates of gains in weight and height among anemic infants and children.

Retrospective studies

In a survey of 2,000 U.S. preschool children, all with birth-weights >2,500 g, Owen (1989) and Owen et al. (1971) reported that children whose heights were below the 25th percentile tended to have lower hemoglobin and transferrin saturation values than children whose heights were above the 25th percentile (Fig. 5). This finding was especially true for children 1 to 3 years of age.

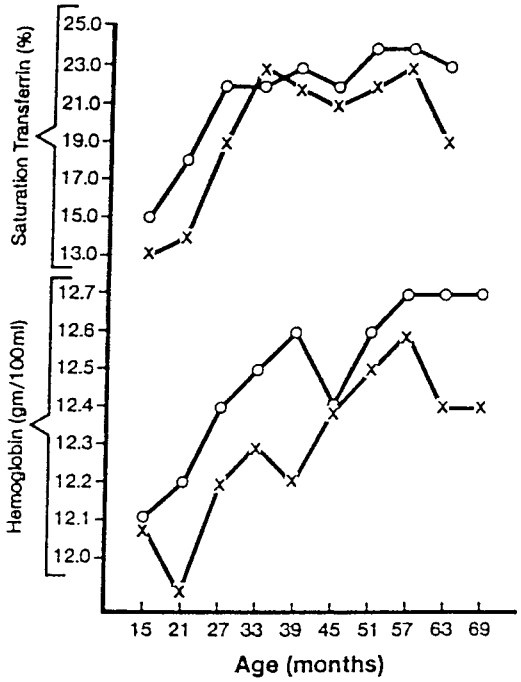

Fig. 5. Hemoglobin and saturation values according to age and stature. X = average hematologic values for children with heights below the 25th percentile. O = Hematologic values for children with heights ≥25th percentile. Redrawn from Owen (1989).

However, children from lower income families accounted for relatively more of the low hemoglobin and transferrin saturation levels. Approximately 25% of infants were breast-fed at 1 week of age and 16% were still breast-fed at 2 months of age (Owen et al., 1971). The type and amount of infant formulas used (non-iron-fortified or iron-fortified) were not identified. Only 5% of infants were given vitamin supplements containing iron. Because detailed dietary intake data were not reported, it was not possible to determine whether the reported decreased growth in stature could be attributed to insufficient caloric/nutrient intake or to the lower hemoglobin and transferrin saturation levels.

Judisch et al. (1966) examined the medical records of 156 infants and children between 12 and 17 months of age who were diagnosed as having moderately severe iron-deficiency anemia (hemoglobin <9.0 g/dL, microcytosis, and hypochromia). One-third of the sample had a birth weight <2,500 g and the majority (86%) were black. For 88 infants, information was available to evaluate the effects of pre- and post-treatment of elemental iron that was provided for 2 months. Treatment with medicinal iron was shown to be associated with accelerated weight gain in the underweight children. Although this study was not a prospective, randomized clinical trial, it provided convincing evidence that growth retardation can be corrected with iron therapy.

Morton et al. (1988) considered iron status of 81 inner-city term infants in London during the first year of life. At one year of age, iron deficiency (hemoglobin >11 g/dL, ferritin <10 μg/L) was associated with feeding >900 ml/d of whole cow and inadequate feedings of solid food. Infants with iron-deficiency anemia at 12 months of age had a greater percentage gain in weight since birth than infants who were not iron deficient. It was suggested that infants with the greater weight gain had become iron deficient because of the demands of growth and an insufficient supply of dietary iron (Morton et al., 1988). However, the amount of foods consumed by infants who were not iron deficient was not reported. Therefore, it was not possible to determine whether iron-deficient infants had a greater weight gain because they consumed more calories than infants who were not iron deficient.

Grindulis et al. (1986) examined 145 Asian children between 21 and 23 months of age. A large percentage (31%) of these children had hemoglobin concentrations <11 g/dL; 57% had plasma ferritin values <7 μg/L, and transferrin saturation values <15%. There was no association between hemoglobin concentration at 22 months of age and body weight at birth or at 22 months of age. However, only the mean values were reported. Hemoglobin and weight gain values for children in the lower quartile of growth were not considered.

Prospective studies

Several prospective studies have reported improved growth of infants who received iron supplementation. In a double-blinded study of iron deficiency without anemia, 75 infants and toddlers aged 6 to 36 months were randomly assigned to receive medicinal iron or placebo (Lamni and Lovric, 1973).

During a 3-month study period, there was a significantly greater gain in mean weight in the iron-treated group than in the control group (1.27 kg vs. 0.68 kg). Although correction of iron deficiency without anemia improved weight gain, only 75 of the 210 children enrolled in the study were evaluated at the end. Additionally, most of the infants in the study initially had acute illness, which may have lowered iron levels and affected weight gain.

In a cohort of infants 3 months of age who randomly received either supplemental iron (10 mg/d) or placebo, Burman (1982) reported that weight gain was significantly greater in the iron-supplemented group than in the non-iron-supplemented group of boys at 21 and 24 months of age. However, iron supplementation did not have a significant effect on girls at any age.

Fifty-four children between 17 and 19 months of age with low hemoglobin levels (8.0–11.0 g/dL) were treated with iron and vitamin C daily for 2 months; 56 children were treated with only vitamin C for 2 months (Aukett et al., 1986). Levels of hemoglobin and related biochemical indices of iron status all improved in the children treated with iron but not in those treated with only vitamin C. Weight gain in the children who received both iron and vitamin C was significant greater than those treated with vitamin C only (10 g/d vs. 7 g/d).

Chwang et al. (1988) reported improved weight, height, and arm circumference growth in anemic (hemoglobin $<$11.0 g/dL) and in iron-deficient (transferrin saturation $<$15%) Indonesian school children who were treated with iron (2 mg/kg/d) for 12 days. Within the control group of non-anemic children, no significant differences were observed between those who were treated with iron and those who received placebo.

The effects of iron supplementation on growth and hematological status of Indonesian anemic (hemoglobin $<$11.0 g/dL and serum ferritin $<$12 µg/L) preschool children aged 2 to 5 years with low weight-for-age were evaluated in a randomized double-blind clinical trial (Angeles et al., 1993). The treatment group received daily supplements of medicinal iron and vitamin C for 2 months. The control group received daily supplements of vitamin C alone. Height and weight of all children increased, but increases in height and height-for-age z-score were larger in the treatment group than in the control group. There were no significant differences in energy intake between the two groups. However, episodes of fever, respiratory infections, and diarrhea occurred more frequently in the control group than in the treatment group for reasons that were not determined; this may have influenced the increased growth rate in the treatment group. Angeles et al. (1993) suggested that the direct action of iron on oxidative processes may have stimulated growth.

Lawless et al. (1994) also showed a significant increase in growth (weight-for-age, height-for-age, weight-for-height, arm circumference, and triceps and subscapular skinfold thicknesses) when 87 primary school children 6 to 11 years of age living in the Shamu village, Coast Province Kenya, were supplemented with medicinal iron (Fig. 6). Children were administered supplemental iron for 14 weeks. Children with severe anemia (hemoglobin $<$8.0 g/dL), heavy hookworm infection, and blood in the urine (indicative of *Schistosoma haematobium* infection) were eliminated from the study. The prevalence of anemia was 75.6% as defined by the WHO hemoglobin cutoff of 12 g/dL. Increases in growth were attributed to an increase in appetite (in terms of calorie intake and the self-reported increase of appetite) in the treatment group. These findings suggest that iron-deficiency anemia may result in temporary anorexia which can be ameliorated with iron therapy.

In a longitudinal study of 276 full-term infants, Stekel et al. (1988) considered mean weight of infants fed milk fortified with 15 mg of iron and infants fed non-fortified milk. Hematological data were comparable in the two groups at 3 months of age when breast-feeding was discontinued, but by 9 months of age, the control group had significantly lower mean hemoglobin, transferrin saturation, serum ferritin, and elevated protoporphyrin. Biochemical differences also were observed at 15 months of age, although there were no differences in mean weight.

In a well-designed double-blind randomized community trial, 219 Mexican preschool children 18 to 36 months of age were

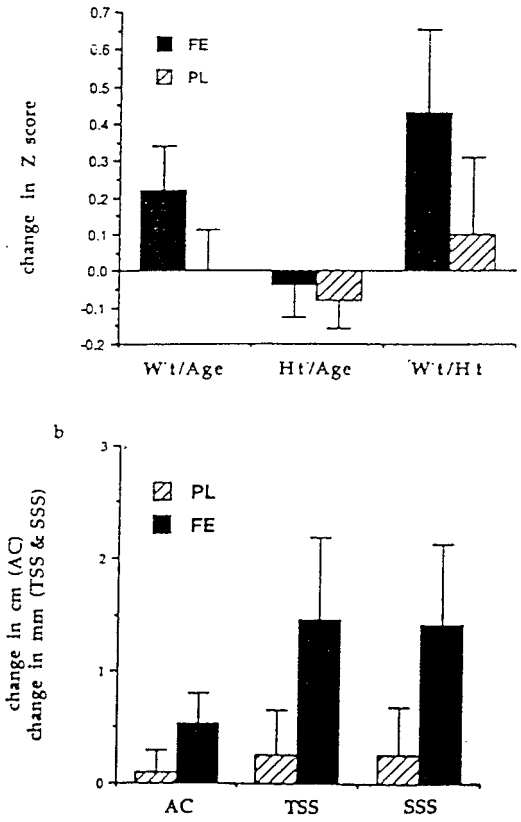

Fig. 6. a: Mean change in z-scores for three anthropometric indicators of growth: weight-for-age (Wt/Age), height-for-age (Ht/Age), and weight-for-height (Wt/Ht) for children in the iron-treated (FE) and placebo (PL) groups (baseline examination − examination 14 weeks later). b: Mean change in arm circumference (AC) triceps skinfold thickness (TSS) and subscapular skinfold thickness (SSS) in children in the iron-treated (FE) and placebo (PL) groups) (baseline examination − examination 14 weeks later). From Lawless et al. (1994).

supplemented with either zinc, iron, zinc + iron, or placebo (Rosado et al., 1997). Children in each group received the supplements for 12 months. The study was conducted in five rural communities in the central highland plateau approximately 150 km northwest of Mexico City. At the beginning of the study, the prevalence of low iron stores (ferritin <12 μg/L) was 43% to 57% in the four groups. At the end of the study, plasma zinc levels increased significantly in the two zinc-treated groups, and plasma ferritin was significantly higher in the two iron-treated groups. The mean hemoglobin level concentration also increased in all groups during the 12-month study period. Zinc and zinc + iron supplementation reduced morbidity but had no significant effect on weight, height, arm circumference, and triceps skinfold thickness.

Idjradinata et al. (1994) studied the effect of iron supplementation on the growth rate in 47 *iron-sufficient* (hemoglobin >12.0 g/dL, transferrin saturation >10%, serum ferritin >12 μg/L) children 12 to 18 months of age in Indonesia. The children were randomly assigned to receive either medicinal iron (3 mg/kg/d) or placebo every day for 4 months. Before treatment, measures of growth (length, weight, and arm circumference) between the two groups were similar. The placebo group showed greater gain in weight than the iron-supplemented group (0.106 kg vs. 0.070 kg) every 2 weeks. The rates of gain in length and arm circumferences did not differ significantly by treatment. Over the entire 4-month period, the differences in gain of weight were not significant. There were no differences in morbidity between the groups. However, the morbidity data were restricted to diagnoses of children who were brought to a health care clinic by their parents. Morbidity data did not include illnesses that were not brought to the attention of the physician; the data also did not reflect the duration and severity of the illnesses in the two groups of young children. Furthermore, food consumption data were not reported. Nevertheless, this study raised the possibility that the widespread practice of iron supplementation in children who are iron sufficient may result in slower weight gain.

The question that still remains is whether the faster growing, term infant is at a greater risk of developing iron-deficiency anemia than those who grow more slowly. It is also not known whether infants who grow more rapidly absorb more iron. Some studies have shown that treatment of iron accelerates gain of weight and height in underweight or stunted children with iron-deficiency anemia. Other studies have reported no short-term differences in rates of growth between infants who were initially iron sufficient or not stunted. One study reported that iron-sufficient children given iron supplements had a significantly lower gain in weight than

those given placebo. It is possible that lack of iron slows growth only after anemia has become severe (Dallman, 1969). However, there is still insufficient information to determine the extent to which iron-deficiency anemia, independent from other nutritional deficiencies, affects infant and childhood growth and development.

IRON-DEFICIENCY ANEMIA AND COGNITIVE DEVELOPMENT

Animal studies

A physiologic basis exists for the relationship between iron status and neurologic function. Specific areas of the brain (the globus pallidus, substantia nigra, putamen, red nucleus, for example) contain concentrations of iron that exceed those found in all other non-hematologic organs, including the liver (Hallgren and Sourander, 1958). Brain iron accumulates from gestation to early adulthood (Tingey, 1977). The total amount of iron in the brain is more sensitive to iron deficiency in early life than in adulthood. Rats made iron deficient during early periods of development do not normalize the amount of iron in the brain even after iron therapy (Dallman et al., 1975; Dallman and Spirito, 1977; Weinberg et al., 1979; Hill, 1988; Youdim et al., 1989; Larkin and Rao, 1990). In contrast, rats made iron deficient as adults normalize the amount of iron in the brain after 1 to 3 weeks of iron therapy (Dallman et al., 1975; Dallman and Spirito, 1977).

Yehuda (1990) and Youdim (1990) have shown that weaning rats made iron deficient have significantly decreased learning ability and altered motor function compared with controls. The long-term decreased learning ability in rats may be related to altered central nervous system neurotransmission (Ruiz et al., 1984). Alternations of neurotransmitters in iron-deficient rats have been linked to the dopamine, serotonin, and GABA (gamma-aminobutyric acid) systems (Ruiz et al., 1984; Youdim et al., 1984).

Dopamine, a major neurotransmitter, is thought to play an important role in cognitive and motor behavior. Iron-deficient rats exhibit a permanent reduction in the number of dopamine D_2 receptors (Ashkenazi et al., 1982; Youdim et al., 1983; Yehuda, 1990; Youdim, 1990). Iron also appears to regulate the level of serotonin in the brain. Iron deficiency lowers serotonin activity which may modulate circadian rhythms, neuroendocrine functions, levels of stress, and motor activity (Youdim et al., 1981, 1983; Youdim, 1990).

In the rat, the brain growth spurt begins within the first postnatal days at about the time neuroblast multiplication ends and when the adult number of neurons has been almost achieved (Dobbing and Sands, 1972). Brain growth spurt ends at about 25 days of age in rats (Dobbing and Sands, 1972). It is noteworthy that learning ability and motor function is altered in rats made iron deficient between gestation and 21 days of age during the critical or sensitive period of the brain growth spurt.

Iron plays an important role in various metabolic processes related to lipids such as oxidative degradation of fatty acids, synthesis of mono- and polyunsaturated fatty acids, plasmalogens, and prostaglandins (Larkin and Rao, 1990). Myelin is composed of 80% lipid and the lipid content of the rat brain triples from birth to 4 months of age (Larkin and Rao, 1990). As compared with controls, 11-day-old iron-deficient rat pups are reported to have reduced myelination of the spinal cord than controls (Larkin and Rao, 1990). Because of the importance of iron in the production of unsaturated fatty acids, it is likely that the fatty acid composition of the myelin lipids in the iron-deficient rat pups is different from that in the controls. Iron deficiency not only reduces the content of myelin in the brain but also produces a change in myelin composition (Larkin and Rao, 1990). To what extent myelination can be corrected by iron supplementation has not been determined. Nevertheless, there is growing evidence that nutritional restriction during the fetal and neonatal development of the rat may produce permanent alterations of the lipid composition of the brain (Dobbing, 1966).

Human studies

Although it is difficult to extrapolate data from animal studies to humans, several studies on infants and children support the association between iron-deficiency anemia

and cognitive delays. In humans, the brain growth spurt is both a prenatal and postnatal event (Dobbing, 1970). Neuroblast multiplication and the adult number of neurons are achieved by the end of the second trimester (Dobbing, 1970). Rapid myelination ends at about 2 years of postnatal life (Dobbing, 1972). The major events of the brain growth spurt, in addition to an increase in size, include the branching of dendritic processes and the establishment of interneural connections (Dobbing, 1972). That deficits in learning ability occur in iron-deficient rats at the time of the brain growth spurt may suggest a similar "period of vulnerability" in infants during which nutritional deficiency may have a lasting effect (Dobbing, 1972, 1990). In humans, this period of vulnerability begins with the third trimester of life and extends to the first 2 years of postnatal life (Dobbing, 1972). During this period, iron-deficiency anemia may have a significant effect of cognitive and behavioral development.

Two studies, one conducted in Santiago, Chile (Walter et al., 1989), and the other in Costa Rica (Lozoff et al., 1987), have provided the most convincing evidence for the relationship between iron-deficiency anemia and cognitive deficits in infants. The Santiago study considered 196 infants in a carefully designed, double-blind, placebo-controlled, prospective trial. Full-term infants from a community health clinic in Santiago were enrolled at 3 months of age and followed to 12 months of age. Breast-fed infants who were spontaneously weaned at 3 months of age randomly received either an iron-fortified milk supplement or the non-fortified milk powder. Iron status (hemoglobin, erythrocyte protoporphyrin, and mean corpuscular volume) of infants was evaluated at 9 and 12 months of age. Infants were classified into three groups: the control group (hemoglobin $>$11.0 g/dL and all other biochemical measures within the normal range); an iron-deficient anemic group (hemoglobin $<$11.0 g/dL and at least two altered biochemical measures); and a iron-deficient without anemia group (hemoglobin $>$11.0 g/dL and at least one altered biochemical measure). At 12 months of age, behavioral and neurodevelopment were evaluated by means of the Bayley Scales of Infant Development (BSID), an accepted index of mental and psychomotor development. Infants with iron-deficiency anemia scored significantly lower than the control and non-anemic iron-deficient groups on both the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). After iron therapy for 3 months, infants who had iron-deficiency anemia still scored significantly lower than the controls in both the MDI and PDI. The performance of the non-anemic iron-deficient infants was indistinguishable from that of the controls.

The Santiago study also considered the relationship between chronicity of iron-deficiency anemia and cognitive development. Infants who had iron-deficiency anemia at both 9 months and 12 months of age (hemoglobin $<$11.9 g/dL at 12 months of age and $<$10.5 g/dL at 9 months of age) were compared with infants who had iron-deficient anemia at 12 months but not at 9 months of age (hemoglobin level $<$11.0 g/dL at 12 months of age but $\geq$10.5 g/dL at 9 months of age). Infants who had iron-deficiency anemia for at least 3 months scored significantly lower on both the MDI and PDI than those who had iron-deficiency anemia only at 12 months of age. Additionally, infants with moderate anemia (hemoglobin = 8.4 to 10.4 g/dL) scored significantly lower on the MDI and PDI than infants with milder anemia (hemoglobin = 10.5 to 10.9 g/dL). All groups of infants with anemia scored lower than the controls. Walter et al. (1989) suggested that the more chronic and more severe the anemia, the more profound were the effects on mental and motor developmental status.

Results from the Bayley motor test indicated that iron-deficient anemic children had more difficulty than the controls and non-anemic iron-deficient children in motor skills related to balance and walking independently. Pollitt (1994) has suggested that a delay in the acquisition of motor skills associated with walking independently is common among children with nutritional deficiencies. Iron-deficient children showed the greatest difficulty in the mental skills related to language acquisition. During the Bayley test, iron-deficient anemic children tended to be less responsive, less attentive,

and less active than infants in the control group.

A multivariate analysis considered the effects of measures of social background, infant growth, and hemoglobin level. Hemoglobin level had the greatest effect on MDI and PDI. A significant effect of recumbent length at 12 months of age was also reported (Walter, 1990).

The Costa Rica Study (Lozoff et al., 1987) considered a cross-sectional sample of 191 children 12 to 23 months of age with various degrees of iron deficiency in a randomized double-blind design. Children were divided into three groups according to their hemoglobin level: iron-deficiency anemia (hemoglobin <10.5 g/dL), intermediate iron deficient (hemoglobin = 10.6 to 11.9 g/dL) and nonanemic (hemoglobin >12.0 g/dL). The BSID were administered before and at both 1 week and 3 months after iron therapy. Before iron therapy, children with iron-deficiency anemia scored significantly lower in both the MDI and PDI than the controls, even after controlling for factors related to birth, nutrition, family background, parental IQ, and home environment. After 3 months of iron therapy, children who had intermediate iron deficiency showed no increase in MDI, but their PDI improved. Significantly lower MDI and PDI scores persisted among the majority of the group of children who had the more severe iron-deficiency anemia. The persistent lower scores suggest that either the iron therapy was inadequate to correct the anemia or that the psychomotor effects are long-lasting, depending on the timing, severity, or chronicity of iron deficiency in infancy (Lozoff et al., 1987).

In the Costa Rica study, iron-deficient anemic infants were described as maintaining closer contact with their mothers, initiating interactions with them more frequently, and spending less time away from them during mother-child play sessions (Lozoff et al., 1987). Mothers were less likely to encourage their children to complete tasks and were less willing to participate during interactions (Lozoff et al., 1986). These observations raise the issue that the presence of environmental risk factors such as poor parent-child interactions before iron deficiency may confuse or amplify the impact that iron deficiency has on infant development.

Recently, Pierano and his associates have considered whether iron-deficiency anemia affects the sleeping behavior of infants (de Andraca et al., 1997). Preliminary results from an analysis of electrophysiologic signals during the sleep-wake cycle of infants suggest that iron-deficient infants' maturation patterns are different from those of iron-sufficient infants. Anemic infants at 6 months of age exhibited a greater level of variability in respiration during sleep and marked motor activity during the initial period of sleep; stabilization was more difficult (de Andraca et al., 1997). Compared with controls (iron-sufficient infants), anemic infants also showed delays in registration of auditory-evoked potentials of the brain stem at 6 months of age. Additionally, central conduction timing was longer. According to de Andraca et al. (1997:128) "these observations suggest that the maturation of the central nervous system (CNS) in anemic infants is delayed." Anemic infants continued to show a delay after receiving prolonged oral iron treatment (up to 6 months of age). As noted above, Larkin and Rao (1990) suggested that iron-deficiency anemia affects CNS development. Alterations in the myelination of the nervous tissue may be the mechanism responsible for some of the neurophysiological delays observed in anemic infants.

De Andraca et al. (1997) have summarized the preliminary results from a large, double-blind, randomized field trial in Chile in which 944 infants were randomly assigned to receive iron-fortified or non-iron-fortified formula at 6 months of age. Only infants with normal iron levels (hemoglobin >10.5 g/dL) were included in the study; anemic children received iron treatment and were excluded. At 12 months of age, a BSID was administered, followed by a complete hematological examination. Among infants fed the iron-fortified formula, 4% had anemia and 15% had iron deficiency; among the unsupplemented group, 24% had anemia and 49% had iron deficiency. No differences were found between the MDI and PDI between the two groups. The preliminary re-

sults seem to suggest that iron supplementation between 6 and 12 months of age did not improve MDI or PDI scores. Although these results seem to contradict those reported in previous studies conducted in Chile and Costa Rica, the exclusion of anemic infants at 6 months of age introduced an important change in the protocol. Iron-deficiency anemia may have a significant effect on cognitive and behavioral development before 6 months of age (de Andraca et al., 1997). In previous studies, the score differences at 12 months of age may have been associated with the chronicity of the anemia that started before 6 months (de Andraca et al., 1997).

These results differ from those reported by Moffatt et al. (1994), who evaluated the efficacy of iron-fortified infant formula in preventing developmental delays and abnormal behavior in Canadian infants. In a double-blind, randomized, clinical feeding trial, 283 almost entirely Native American infants from very-low-income Canadian families were fed one of two infant formulas with differing levels of iron (12.8 mg/L vs. 1.1 mg/L). Iron status was measured by venous blood sampling at 6, 9, 12, and 15 months of age. The BSID was administered at the same time intervals when the blood was drawn. The groups were initially comparable in iron status, growth, and social variables. Differences in iron status were observed at 9 to 12 months. PDI scores differed between groups at 9 and 12 months of age but not at 6 or 15 months of age. MDI scores were not affected. It was suggested that iron-fortified infant formula significantly reduced iron deficiency and prevented a decline of psychomotor development in a high-risk group of infants.

In a cross-sectional study of the association between hemoglobin level and childhood behavioral problems, 236 Hispanic children 2 to 5 years of age living in low-income census tracts in Los Angeles (Johnson et al., 1992) were evaluated. Venous blood samples were analyzed for hemoglobin, mean corpuscular volume, free erythrocyte protoporphyrin, and lead. Child behavior checklists were developed to assess a variety of behavioral problems (social withdrawal, sleep problems, depression, aggression, and hyperactivity). The prevalence of anemia (hemoglobin $<$11.5 g/dL) in 2- and 3-year-old girls and boys was high (16% to 23%), but the prevalence was lower in 4- and 5-year-old girls and boys (0 to 8%). A significant correlation between decreasing hemoglobin values and increasing behavior problems was found in girls but not in boys. It was unclear why significant associations between hemoglobin level and adverse behaviors were found only in girls. An important limitation of this study was its cross-sectional design. Hemoglobin concentration and behavior were recorded at only one point in time. It was not possible to determine whether the changes in hemoglobin occurred before changes in behavior. It was also not possible to determine the severity of iron deficiency because other biochemical measures (e.g., serum ferritin, erythrocyte protoporphyrin, etc.) were not obtained. Furthermore, other social factors attributable to an impoverished neighborhood were not considered in the analysis, making the results difficult to interpret.

Long-term effects of iron-deficiency anemia

Two follow-up studies have described the cognitive performance of 5- to 6-year-old children who were iron-deficient anemic as infants in previous studies (Lozoff et al., 1987; Walter et al., 1989). The Chile study (de Andraca et al., 1990) included infants who had iron-deficiency anemia at 12 months of age or had normal iron status. Logistic regression analyses provided a measure of the relative risk of poorer performance for infants who had iron-deficiency anemia while controlling for maternal education, neurologic maturity, home environment, attendance at nursery school, and duration of breast-feeding. At 5.5 years of age, children who had iron-deficiency anemia at 12 months of age had significantly lower scores than the non-anemic controls in tests that evaluated intellectual, linguistic, motor, psychoeducational, and visiomotor integrative abilities (Table 7). Although the study suggested that iron-deficiency anemia in infancy may have a lasting effect, the control group received more environmental stimulation in their homes with respect to language and academic behavior, and affection. The differ-

TABLE 7. Cognitive abilities of 5.5-year-old children who had iron-deficiency anemia as infants compared with a control group of non-anemic children[1]

	Formerly anemic group (n = 41)	Control group (n = 29)	*P*
Age (months)	66.0 ± 2.3	67.0 ± 5.7	NS
IQ	87.0 ± 6.0	92.7 ± 8.3	0.02
Psychoeducational abilities			
Standard score	26.6 ± 18.9	41.3 ± 22.9	0.01
Visual-motor integration			
Standard score	7.8 ± 2.5	9.0 ± 2.2	0.01
Motor proficiency			
Fine motor	39.6 ± 7.5	44.1 ± 6.9	0.01
Gross motor	37.4 ± 8.5	41.1 ± 7.3	NS
Global composite	38.7 ± 9.1	44.3 ± 8.3	0.01
Language abilities	82.0 ± 11.0	88.5 ± 7.4	0.01
Hemoglobin at 12 months	10.1 ± 0.7	13.0 ± 0.8	0.01
Hemoglobin at 15 months	12.8 ± 0.7	13.0 ± 0.7	NS

[1] Data from de Andraca et al. (1990).

ence in the quality of the child's environment in a child's development raises the question as to whether the differences in test scores actually reflected iron-deficiency anemia or other environmental factors.

In the Costa Rica study (Lozoff et al., 1991) 85% of the 191 children in the original study underwent comprehensive clinical, nutrition, and psychoeducational evaluation at 5 years of age. Children who had moderately severe iron-deficiency anemia (hemoglobin ≤10 g/dL) had lower scores on tests of mental and motor function than the rest of the children, even after controlling for a comprehensive set of background factors including demographic characteristics, birth history, nutritional status, socioeconomic status, level of stimulation in the home, and parental IQ. The authors suggested that children who had iron-deficient anemia in infancy had a greater risk for developing long-lasting behavioral changes.

The same team of investigators (Lozoff et al., 1996) considered whether extended oral iron therapy can correct lower developmental tests scores in infants with iron-deficiency anemia. In a cross-sectional, double-blind controlled trial in Costa Rica 32 12-to-23-month-old infants with iron-deficiency anemia and 54 non-anemic controls were examined. The iron-deficient anemic infants were treated with iron therapy for 6 months. Half the non-anemic infants were treated with iron therapy and half with placebo. Developmental test scores and iron status were determined before treatment, and after 3 months and 6 months of treatment. At all three time points, iron-deficient anemic infants scored lower on mental tests than the non-anemic infants. There were no reported significant differences in motor test scores. However, the anemic infants came from families with lower maternal education and provided less support for child development; they were also less likely to be breast-fed, were weaned earlier, and consumed more cow milk. As in the follow-up study in Chile, the differences in the quality of the home environment raised the question as to whether the lower mental tests scores in the iron-deficient children were the result of their anemia. Lozoff et al. (1996) suggested that iron-deficiency anemia served as a *marker* for a variety of nutritional and family problems that negatively affected infant development. Thus, despite extended oral iron therapy and an excellent hematologic response, it was not possible to demonstrate conclusively that iron deficiency alone was associated with lower mental scores.

The Costa Rica study (Lozoff et al., 1996) was also limited by the fact that it was not a prospective, controlled clinical feeding study; groups differed significantly with respect to mother's education level, mother's age, and stimulation in the home at study entry. It was not possible to determine when and for how long iron deficiency was present before treatment. To demonstrate that iron deficiency is indeed related to long-term deficits in mental and motor development, it would require the examination of a placebo-treated anemic group.

The lack of a treatment effect contrasts with a recent study in Indonesia (Idjradinata and Pollitt, 1993) where significant and large increases in test scores after iron treatment (19 points in mental scores and 24 points in motor scores) were observed. Iron-deficient anemic infants 12 to 18 months of age were randomly assigned to receive ei-

ther oral iron therapy or placebo for 4 months. Minimal changes were observed in the placebo-treated anemic infants. The results seem to suggest that the effects of iron deficiency may not be necessarily long-term. As compared with the Costa Rica study (Lozoff et al., 1996), the reasons for the differing results cannot be explained by the duration of treatment (4 or 6 months) or by the severity of iron-deficiency anemia because iron status and infant age were similar in both studies at study enrollment. Lozoff et al. (1996) suggested that the Costa Rican families may have been more disadvantaged than the Indonesian families. The more disadvantaged the conditions the more likely the effects of iron-deficiency anemia may persist over time even after iron treatment. Although there remain many important unanswered questions regarding a causal relationship between iron-deficiency anemia and lower developmental test scores, prevention of iron-deficiency anemia seems to be the most appropriate strategy to take considering the theoretical possibility that the effects of iron-deficiency anemia are irreversible in some infants (Lozoff, 1990).

To be sure, behavior and developmental changes observed in iron-deficient infants are probably related and intensified by other environmental factors that impair normal development (de Andraca et al., 1997). In poor families, biological and environmental risk factors coexist (Huston et al., 1994). In conditions of widespread dietary iron insufficiency both mothers and their infants may be iron deficient. Iron-deficient mothers may show a lower level of activity, attention span, and motivation during infant-mother interactions (Allen, 1997). These effects in turn could have a negative long-term impact on infant cognitive development. Other risk factors associated with impaired infant cognitive development include low birth-weight, malnutrition, maternal depression, and low parental education level (Pollitt, 1987; Zuckerman and Beardslee, 1987; Lyons-Ruth et al., 1991; Breslau et al., 1994). The studies described above have not been able to elucidate in detail all the biological and social factors associated with iron-deficiency anemia and delayed cognitive development during infancy. The data do not allow the formulation of a causal relationship, only an associative relationship (de Andraca et al., 1997). Additional research is clearly necessary.

IRON-DEFICIENCY ANEMIA AND INFECTION

Effects of infection on iron status

Chronic infection or the inflammatory response can cause anemia (Beutler, 1988; Yip and Dallman, 1988). Even mild infections associated with common childhood illnesses such as upper respiratory infections, gastroenteritis, and otitis media can lower hemoglobin concentration and transferrin saturation, and increase serum ferritin concentration (Reeves et al., 1984; Beutler, 1988; Yip et al., 1987). Decreases in hemoglobin concentration and transferrin saturation and an increase in iron stores occur because the reticuloendothelial system retains an increased proportion of iron from senescent erythrocytes (Cartwright and Lee, 1971); there is also decreased absorption of iron from food (Beresford et al., 1971). Associated with the increase in ferritin concentration is a reduction of erythrocyte survival, and probably a decrease in serum erythropoietin production (Lee, 1983). Because serum ferritin is no longer a measure of body stores of iron it is difficult to distinguish anemia from infection from that associated with iron deficiency. However, Cook (1992) has reported that, in adults, when anemia is associated with infection, serum ferritin concentration is typically >50 μg/L in the absence of iron deficiency and <50 μg/L in the presence of iron deficiency. Nevertheless, serum transferrin receptor should be used to measure iron nutritional status because it is not influenced by chronic infection or inflammation (see above).

Mild viral infection in infants induces a significant decrease in hemoglobin that may persist to 30 days (Olivares et al., 1989). Twelve-month-old infants who were immunized with live attenuated measles virus were studied prospectively for 30 days. Hemoglobin concentration decreased significantly (0.6 g/dL to >1.0 g/dL) by 9 to 14 days in 23.3% of the infants. Serum iron and transferrin saturation also decreased, but serum ferritin increased significantly. Of the

36 infants whose blood samples were obtained at 30 days after vaccination, four became anemic by day 9, and three continued to have low hemoglobin concentrations (hemoglobin <11.0 g/dL) until day 30, even though the group mean hemoglobin value returned to baseline. Thus, the effects of mild to moderate acute febrile illnesses must be considered when evaluating hematologic status. Several specific viral processes known to accompany anemia have been described by Birgegard et al. (1978) and Baranski and Young (1987).

In two retrospective studies, children who had a history of mild infections during the previous 1 to 3 months had a higher incidence of anemia and sedimentation rate, particularly infants younger than 12 months of age (Reeves et al., 1984; Jansson et al., 1984). Olivares et al. (1995) evaluated the hematological status of children between the ages of 6 months and 10 years who were seen for common acute febrile infections in an outpatient health clinic. A blood sample was obtained at the time of diagnosis and after 30 days. During the infection, there was a significant decline in hemoglobin, serum iron, and transferrin saturation, and a significant increase in serum ferritin (Olivares et al., 1995).

Many children with high blood levels of lead also have evidence of iron deficiency (Yip et al., 1981). Lead poisoning is associated with a defect in the utilization of iron. Possibly 1.5% of children in metropolitan areas of the United States have blood levels above 15 µg/dL (Mitchell and Baburich, 1987). Lead poisoning also has been known to occur in villages in the Middle East and elsewhere because stones used to grind cereal grains contain lead (Wadsworth, 1992).

Iron and the immune system

The literature on the relationship between iron-deficiency anemia and immunity is controversial. Some researchers support the hypotheses that mild anemia is beneficial for immunity because it inhibits bacterial growth of microorganisms. Other researchers argue that any inadequate supply of iron to body tissues is detrimental to immunity. The hypothesis that an iron-enriched cellular environment in the host predisposes to infection raises questions about the safety of the routine and widespread use of iron administration, including the small amounts of iron present in infant foods (Sussman, 1974; Pearson and Robinson, 1976; Weinberg, 1992a).

It is well established that iron plays an important role in the metabolism of many bacterial species (Bullen et al., 1972, 1978; Weinberg, 1978, 1984). At the turn of the century, Trousseau (1882) observed that iron supplementation of patients with tuberculosis often caused a recurrence of the disease. Iron is essential for the multiplication of bacteria because the iron-containing enzyme ribonuclease reductase is required for DNA synthesis (Dallman, 1989). Administration of iron under certain laboratory conditions may enhance multiplication of microorganisms to the detriment of the host.

Several studies have suggested the existence of an anti-infective defense system termed "iron withholding" (Barry and Reeve, 1977; Murray et al., 1978; Oppenheimer et al., 1986; Weinberg, 1992a, 1992b) whereby there is an attempt to deny the availability of iron to microbial pathogens and neoplastic cells. Specifically, transferrin and lactoferrin are believed to inhibit the growth of bacteria by their ability to bind iron so tightly that very little is available to support the growth of microorganisms (Bullen et al., 1972, 1978; Weinberg, 1978, 1984, 1992a). Weinberg (1992a) has indicated that the iron-withholding system can be compromised by either an excessive intake of iron or the interference with the synthesis of various iron-binding proteins. A compromise of the iron-withholding response is the reason for the concern that iron supplementation may predispose a host to infection.

The studies by Murray et al. (1975a, 1975b, 1978) are often cited as evidence for the protective effect that iron deficiency has on infection. In a prospective randomized study of 137 iron-deficient adult Somali nomads, 67 of whom were treated with placebo and 71 with medicinal iron (900 mg of oral ferrous sulfate) for 1 month, seven episodes of infection occurred in the placebo group and 36 in the treated group (Murray et al.,

1978). These 36 episodes included activation of existing malaria, brucellosis, and tuberculosis. It appears that iron-deficiency anemia in this population was associated with suppression of signs of active infection, especially intracellular infections. Iron-deficiency anemia in the Somali nomads was attributed not to intestinal parasites, which are rare in nomads, but to poor intake of dietary iron. Murray et al. (1978) suggested that iron deficiency in Somali nomads may be part of an ecological compromise. Animal milk, low in iron, is the major source of energy and the cause of chronic iron-deficiency anemia. Iron-deficiency anemia, although debilitating, is rarely fatal, but it prevents the more serious consequences of the potentially fatal infections associated with malaria, tuberculosis, and brucellosis. Although this study has been criticized because it was not double-blind, it offers the most convincing evidence that oral iron treatment may increase the activation of certain infectious diseases.

A tendency for malarial activation with iron treatment has also been reported by Masawe et al. (1974) in Tanzania. McFarlane et al. (1970) also attributed increased mortality from infection in kwashiorkor to iron treatment. A significant association between serum transferrin saturation concentration and survival was observed in a sample of 40 children aged 15 to 5 years who were administered a high-protein diet, antimalarial agents, and iron. Infection was the most frequent cause of death. After 2 weeks of treatment, *Staphylococcus aureus* grew more readily in the serum of children with kwashiorkor. Mortality was much higher among children with low levels of transferrin saturation (30 mg/dL) than among those with higher levels (130 mg/dL) (McFarlane et al., 1972). McFarlane et al. (1972) suggested that in patients with low transferrin saturation, iron therapy resulted in an increase in free iron that promoted bacterial growth. However, those who died had more severe kwashiorkor and suffered from a variety of other medical and nutritional problems; the low transferrin saturation probably reflected the severity of the illness and not the iron supplementation.

In vivo studies of parenteral iron supplementation have considered the role of iron in promoting bacterial growth in infants. In New Zealand, between 1970 and 1972, iron-dextran was administered routinely soon after birth to prevent iron-deficiency anemia in Polynesian infants (Cantwell, 1972). The incidence of *E. coli* meningitis and septicemia was observed to be higher (22 per 1,000 infants) during the 2-year period when injections of iron-dextran were routinely administered than in the following 2-year period (1973 to 1974; 1.8 per 1,000 infants) when injections of iron-dextran were discontinued (Barry and Reeve, 1977). However, this study is flawed because the entire population was treated with iron-dextran and there were no controls. Further, the prevalence of iron deficiency over time was not documented.

In a well-designed, doubled-blind, longitudinal study conducted by Oppenheimer et al. (1986) in Papua, New Guinea, 486 newborns were randomly assigned to receive either 150 mg of elemental iron as intramuscular iron dextran or a placebo at 2 months of age. After 6 months of follow-up, 18.5% of the iron-treated group and 11.3% of the controls were positive for malaria. After 12 months, the percentages of malaria were 33% and 20%, respectively.

In contrast to the studies by Barry and Reeve (1977) and Oppenheimer et al. (1986) there was no increase in the incidence of infection in a U.S. study in which premature infants were given iron dextran (Leikin, 1960). Additionally, in a Finnish study, lower infection rates during the first 6 months were observed in newborns given iron dextran than in untreated controls (Salmi et al., 1963).

In general, the best evidence that iron supplementation promotes infection is in populations where malaria is present. However, the infection rate of malaria and the ability to detect it are not synonymous (Walter et al., 1989). In the pathogenesis of malaria, newer red blood cells are more susceptible to infection. Thus, it is possible that "iron-deficient infants do not have as heavy a burden of parasitemia as do the iron-replete infants and that actual infection rates are similar" (Walter et al., 1997: 113). Most studies that support the hypoth-

esis that iron treatment contributes to increased risk of infection are based on data from disadvantaged populations living in impoverished conditions. In these populations, other coexisting nutritional deficiencies may also play a role in the susceptibility to infection.

Evidence that oral iron supplementation provides protection against infection

Several clinical studies have suggested that administration of iron in the form of iron-fortified foods or medicinal iron does not increase the risk of infection in healthy infants. Over 60 years ago, Mackay (1928) reported the results of a nutrition survey of 154 infants living in London. In the 1920s, most infant were fed human milk or cow milk. Mackay (1928) indicated that anemia was common and that iron supplementation was required. Compared with controls, infants who were provided oral supplementation of iron had a higher mean hemoglobin level; the incidence of respiratory and diarrheal disease decreased by 50%. However, the study did not consider any potential confounding variables and did not have concurrent treatment groups. Nevertheless, Mackay's recommendation that formula-fed infants be given supplemental iron before 2 months of age and her observation that many breast-fed infants also require supplemental iron were insightful and prophetic.

Andelman and Sered (1966) compared the effects of iron-fortified and non-iron-fortified infant formula on rates of infection in two large groups of infants from low-socioeconomic families: 603 infants were fed iron-fortified formula and 445 control infants were fed non-iron-fortified formula. Seventy-six percent of infants who did not receive the iron-containing formula developed iron deficiency compared with 9% in the group fed iron-fortified formula. Significantly fewer respiratory infections were observed in the infants who received iron than those who did not. This study was criticized because the definition for infection was not clear and the infection rates were determined from parental recall rather than from physician examination.

Recently, Walter and his colleagues (1997) reported the results from three field trials in Chile that considered the effect that iron-fortified foods had on the incidence of infection. In the first field trial, infants were randomly assigned to an iron-fortified formula group or a non-iron-fortified group at 3 months of age when they were partially or fully weaned from the breast. Juices were introduced at 2 months of age, vegetables and meats at 4 months, legumes at 6 months, and table foods at 9 months. Infants with hemoglobin levels <9 g/dL at 9 months of age were excluded from the study. Data were available for 53 infants receiving iron-fortified formula and 47 receiving non-iron-fortified formula. The prevalences of anemia and iron-deficiency were significantly less in the iron-fortified group than in the non-iron-fortified group at 9 or 12 months of age. The mean number of episodes of diarrhea and lower respiratory infections were not significantly different between the feeding groups.

The second field trial was conducted to determine whether the results of the first field trial could be replicated. Detailed medical and nutritional status information was collected for 585 infants who received non-iron-fortified formula and 654 infants who received iron-fortified formula. At 9 and 15 months of age, laboratory tests of iron status were performed on a subsample of 200 infants in each feeding group. As in the first field trial, the percentage of iron-deficient infants was lower in the iron-fortified group. During the summer months, when diarrhea was more prevalent, the iron-fortified formula group had a lower incidence of diarrhea than the group receiving non-iron-fortified formula. No group differences in the incidence of diarrhea were observed in the winter months. Additionally, there were no seasonal differences in the incidence of respiratory infections between the two feeding groups.

The third field trial added an evaluation of the effects that iron-fortified infant cereal (Heresi et al., 1995) had on rates of infection. Three-month-old breast-fed infants were randomly assigned to a group receiving heme-iron-fortified rice cereal as a weaning food at 4 months of age or to a group provided with the common solid foods that Chilean infants typically receive (a meat-cereal-vegetable soup, fruit, and fruit juice

at 4 months, legumes at 6 months, and table foods at 9 months). Infants who were weaned from the breast were assigned either to a group receiving iron-fortified formula or to a group receiving non-iron-fortified formula. Infants were followed to 12 months of age. Iron-deficiency anemia as defined by low serum ferritin and hemoglobin values decreased in incidence across the feeding groups as follows: non-iron-fortified infants weaned early, breast-fed infants not fed iron-fortified cereal, breast-fed infants fed iron-fortified cereal, and infants fed iron-fortified formula and iron-fortified cereal. These results indicated the partial protection offered by human milk and the effectiveness of feeding iron-fortified foods beginning at 3 to 4 months of age. The incidences of diarrhea and upper respiratory disease were identical in all groups (Walter et al., 1997).

In summary, in developing countries where sanitation and poor living conditions increase the risk of infectious disease, only one study demonstrated that parenteral iron administered in 2-month-old infants moderately increased the incidence of certain illnesses, specifically malaria. However, the extent to which other nutritional deficiencies also contributed to the incidence of illness was not established. All current information indicates that iron fortification of foods is not associated with increased incidence of disease. There is some evidence that an adequate supply of iron may be beneficial to immunity.

Supplemental oral iron and mild infection

Is it necessary to discontinue the administration of supplemental iron for those infants who have contracted mild infections? According to the American Academy of Pediatrics (1978) this is probably unnecessary because "(1) relatively modest amounts of iron are present in most fortified foods, (2) iron absorption is probably decreased by infection, and (3) the major source of serum iron is the reticuloendothelial system rather than the diet." Iron supplementation at recommended levels for infants appears to have a small effect on transferrin saturation (Andelman and Sered, 1966). When groups of infants were either unsupplemented or supplemented with medicinal iron (≥2 mg/kg/d in preterm infants and 1 mg/kg/d in term infants) the difference in transferrin saturation averaged 3% to 10% and did not exceed 30% (Andelman and Sered, 1966; Melhorn and Gross, 1971; Brozovic et al., 1974). In vitro evidence of decreased bacteriostatic activity has been shown to be associated with a transferrin saturation exceeding 60% to 80%. Thus, the slight elevation in serum iron level resulting from iron-fortified foods is unlikely to be of any concern for normal, healthy infants (American Academy of Pediatrics, 1978). However, it is difficult to come to any firm conclusions concerning the administration of parenteral iron, but it seems reasonable to provide oral iron only, except for specific indications (American Academy of Pediatrics, 1978) such as when malaria is endemic.

Lactoferrin and gastrointestinal flora

Lactoferrin is believed to play a role in the suppression of bacterial growth in the intestinal tract (Bullen et al., 1972). Based on in vitro studies with human milk and in vivo studies with newborn guinea pigs, Bullen et al. (1972) have reported that lactoferrin in combination with specific antibodies against *E. coli* has a bacteriostatic effect in the intestinal tract. Large doses of oral iron in the form of heme iron (hematin) given to newborn guinea pigs enhanced the growth of *E. coli* (Bullen et al., 1972). Mevisson-Verhage et al. (1985) reported that the number of *E. coli* was greater and the number of bifidobacteria less in feces of infants fed iron-fortified formula than fed non-iron-fortified formula. These findings suggest that feeding iron-fortified formula diminishes the ability of infants to resist gastrointestinal infections. However, as Fomon (1993: 250) has pointed out, "if withholding iron from gastrointestinal organisms was an important means of protecting the infant against gastrointestinal infections, one would anticipate that the non-iron-supplemented breast-fed infant would be much less susceptible to such infections than the iron-supplemented, breast-fed infant, and that infants fed non-iron-fortified formulas would be less susceptible to gastrointestinal infections than infants fed iron-fortified formula." There are no convincing data that

support this argument (American Academy of Pediatrics, 1978; Stockman, 1981; Humbert and Moore, 1983; Dallman, 1989).

Tolerance of iron-fortified formula

If increased iron has an undesirable effect on the infant's intestinal flora, it could be hypothesized that breast-fed infants given iron-fortified formula should have more episodes of diarrhea than infants fed a low-iron formula. Scariati (1997) compared the frequency of diarrhea in infants grouped into five feeding categories: exclusive breastfeeding, human milk and iron-fortified formula, human milk and low-iron formula, exclusive iron-fortified formula, and exclusive low-iron formula. The analyses adjusted for the infant's age and gender, mother's education, occupation, smoking history, household size, household income, and day care use. Information about feeding and diarrheal episodes were collected from 2 to 12 months of age. The rates of diarrhea were similar in groups of infants fed iron-fortified formula or low-iron formula. Infants fed formula only (iron-fortified and non-iron formulas combined) had a significantly higher rate of diarrhea than infants exclusively breast-fed. Infants who received both human milk and formula also had a significantly higher rate of diarrhea, but it was lower than that of infants fed formula only. There were no reported differences in the rates of diarrhea between breast-fed infants given iron-fortified formula and those given low-iron formula. This later finding suggests that although supplementation with iron may affect the intestinal flora of the breast-fed infant, "the change was physiologic, not pathologic" (Scariati et al., 1997). The study also indicated that among infants given formula only, those fed iron-fortified formula had a significantly lower rate of diarrhea than those fed low-iron formula. This suggests that among infants fed formula, iron-fortification provided a small but significant protection against diarrhea (Scariati et al., 1997). Based on the results of this study, the authors concluded that there is no convincing evidence to recommend using low-iron formula for infants who are not breast-fed. Recently, prospective cohort studies have indicated significant differences in the rates of diarrhea (of undeterminable cause) between formula-fed infants and those fed human milk (Dewey et al., 1995). In the first year of life the incidence of diarrheal illness among breast-fed infants was half that of formula-fed infants (14% vs. 31%). However, during the second year of life the incidence of diarrhea was similar between groups.

There are anecdotal reports that infants fed iron-fortified formula are more prone to fussiness and constipation; some physicians seem reluctant to recommended feeding iron-fortified formulas. In three crossover studies in which infants were fed iron-fortified formula during some time periods and non-iron-fortified formula during other periods, infant's behavior (fussiness, cramps, regurgitation, flatus, colic) was compared (Nelson et al., 1988). Two of the three crossover studies were doubled-blind. No significant differences were reported, except for stool color; dark-colored or greenish stools were more frequently associated with the iron-fortified formula. Oski (1980) also reported no significant differences between infants fed either an iron-fortified formula or a non-iron-fortified formula with respect to tolerance to the feedings, abdominal cramps, or stool characteristics.

JUSTIFICATION FOR CONTINUED IRON SUPPLEMENTATION

Infants are one of the most vulnerable groups to develop iron-deficiency anemia due to their rapid growth and expansion of blood volume at a time when their diet may consist of a marginal supply of iron. Although iron-deficiency anemia is still a major problem in certain populations of American infants, the prevalence of iron-deficiency anemia in the United States has decreased dramatically over the past 20 years. This recent decline has been attributed to the general improvement in iron nutrition as the result of the increased use of human milk, iron-fortified infant formulas, and iron-fortified infant foods. Among children in the WIC program, the prevalence of iron-deficiency anemia has decreased significantly because WIC mandates the use of iron-fortified formula for bottle-fed infants eligible for the program. Both the American Academy of Pediatrics (1989) and the Euro-

pean Society for Gastroenterology and Nutrition (ESPGAN, 1990) recommend that infants receive only human milk or iron-fortified formula as the milk feeding throughout the first year of life. In healthy, breast-fed infants the addition of iron-fortified infant foods after 6 months of age is recommended (American Academy of Pediatrics, 1976).

The relationships between iron fortification and potential changes in intestinal bacterial flora and binding of lactoferrin in human milk resulting in colonization with *E. coli* are of interest but have not been clearly demonstrated; these await further consideration. For infants who are not breast-fed, an iron-fortified infant formula is appropriate throughout the first year of life. There is no convincing evidence to support the use of a low-iron-fortified infant formula during infancy. In the United States, there may be significant public health consequences if iron fortification during infancy is discontinued or modified in any way; an unknown percentage of infants may be at risk to later develop iron-deficiency anemia.

The evidence that iron-deficiency anemia is associated with deficits in infant motor and mental developmental status must not be overlooked even though such deficits may be reversed with iron therapy or may reflect the influence of environmental adversity. Case-control studies show an association between iron-deficient anemic infants and impairment of psychomotor development. Alterations of sleep patterns and auditory-evoked potentials are also associated with iron-deficiency anemia. The analyses of infant neurophysiological processes represent novel approaches that may provide greater insight into the mechanisms involved in iron deficiency and behavior.

For infants in countries where chronic infection is commonplace, there should be careful consideration of how much iron is actually obtained from the diet. Iron-deficiency anemia may be a symptom of a number of different pathological conditions, each of which may have multiple origins. Studies on iron-deficiency anemia should include observations not only on hemoglobin levels but also on the presence or absence of hemorrhage, chronic disease, and hemoglobinopathies. When possible, transferrin receptor levels should be measured so that anemia from infection can be distinguished from anemia of iron deficiency.

At present, the benefits of oral supplementation of iron outweigh the possibility of iron excess during a period of growth and development characterized by marginal dietary intakes of iron. To date, only in a few studies where malaria is endemic has an increased risk of infection been linked to the use of iron supplementation. Oral iron supplementation appears to provide a safe and effective means to prevent iron-deficiency anemia in all infants. The attributes of breast-feeding are also evident not only for the prevention of iron deficiency but because of the immunological benefits it confers to infants.

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